ACP | MKSAP® 19

Medical Knowledge Self-Assessment Program®

Pulmonary and Critical Care Medicine

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

Welcome to the Pulmonary and Critical Care Medicine Section of MKSAP 19!

In these pages, you will find updated information on pulmonary diagnostic testing, airways disease, diffuse parenchymal lung disease, occupational lung disease, pleural disease, pulmonary vascular disease, lung tumors, sleep medicine, high-altitude–related illnesses, critical care principles and utilization issues, common ICU conditions, and other specific critical care topics. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of pulmonary and critical care medicine.

MKSAP 19 strives to provide the clinical knowledge its learners need to navigate their longitudinal learning paths. MKSAP 19's core content contains essential, newly researched information in 11 subspecialty areas of internal medicine–created by dozens of expert generalists and subspecialists. Development of MKSAP 19's syllabus and its 1200 all-new, peer-reviewed, psychometrically validated multiple-choice questions (MCQs) has been informed by ABIM Certification and Maintenance of Certification (MOC) requirements, emerging internal medicine knowledge, and our learners' feedback. MKSAP 19 continues to include *High Value Care* (HVC) recommendations and MCQs, based on the concept of balancing clinical benefit with costs and harms. Hospital-based internists can continue to trust that MKSAP's comprehensive hospitalist content, integrated throughout the syllabus, and hospitalist-focused MCQs, specially designated with the blue hospitalist icon (H), continue to align with the ABIM's Focused Practice in Hospital Medicine MOC exam blueprint and enhance learning for hospital-based practitioners.

More than ever before, MKSAP 19 Digital focuses on individualized learning and convenience. In addition to custom quizzes and interlinked questions and syllabus sections, MKSAP 19 Digital's new learning dashboard enables users to create a self-directed learning plan, with topic-specific links to resources within MKSAP and ACP Online. Multimedia formats, including whiteboard animations and clinical videos, will benefit our audiovisual learners, while MKSAP's Earn-as-You-Go CME/MOC feature now allows subscribers to earn CME/MOC as they answer individual questions. In addition to Extension Questions and New Info Updates, MKSAP 19 Complete and Complete Green continue to offer Virtual Dx and Flashcards and now offer brand-new enhancements: MKSAP Quick Qs, a set of concise questions mapped to high-frequency/high-importance areas of the ABIM blueprint mirroring boards-style MCQs, and an embedded digital version of Board Basics for easy-access exam prep.

Language can be imprecise and imperfect, but MKSAP 19's Editors and contributors commit to using language and images that support ACP's commitment to being an anti-racist organization that supports diversity, equity, and inclusion throughout health care and health education. ACP also continues to ensure diversity among MKSAP's physician-contributors. When appropriate, the MKSAP Editors also rely on MKSAP 19 Digital's expanded use of multimedia enhancements, including video and audio, to explore and more fully explain issues surrounding the presentation of MKSAP 19 clinical content as it relates to race and ethnicity. MKSAP 19 users are encouraged to contact the Editors at mksap_editors@acponline.org to help us identify opportunities for improvement in this area.

On behalf of the many internists and editorial staff who have helped us create our new edition, we are honored that you have chosen to use MKSAP 19 to meet your lifelong learning needs.

Sincerely,

Davoren Chick, MD, FACP
Editor-in-Chief
Senior Vice President
Medical Education Division
American College of Physicians

Pulmonary and Critical Care Medicine

Committee

Rendell W. Ashton, MD, FACP, Section Editor
Associate Professor of Medicine
Cleveland Clinic Lerner College of Medicine of the Case Western Reserve University
Associate Designated Institutional Official/Associate Director, Graduate Medical Education
Program Director, Pulmonary and Critical Care Fellowship
Cleveland Clinic
Cleveland, Ohio

Sean M. Caples, DO, MS
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Mayo Clinic College of Medicine
Rochester, Minnesota

Neal F. Chaisson, MD
Program Director, Critical Care Medicine Program
Cleveland Clinic
Cleveland, Ohio

Melissa King-Biggs, MD
Department Chair, Pulmonary and Sleep Medicine
HealthPartners Medical Group
Assistant Professor
University of Minnesota School of Medicine
St. Paul, Minnesota

Eduardo Mireles-Cabodevila, MD
Director, Medical Intensive Care Unit
Medical Director, Simulation and Advanced Skills Center
Cleveland Clinic
Cleveland, Ohio

Tathagat Narula, MD
Consultant, Lung Transplant
Division of Transplant Medicine
Medical Director, Adult Cardiopulmonary Rehabilitation Unit
Assistant Professor of Medicine
Mayo Clinic College of Medicine
Jacksonville, Florida

Darlene R. Nelson, MD, MHPE
Program Director, Pulmonary and Critical Care Medicine, Critical Care Internal Medicine, and Pulmonary Disease Fellowships
Assistant Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Mayo Clinic College of Medicine
Rochester, Minnesota

Gretchen Renae Winter, MD
Assistant Professor
Department of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Editor-in-Chief

Davoren Chick, MD, FACP
Senior Vice President, Medical Education
American College of Physicians
Philadelphia, Pennsylvania

Senior Deputy Editor

Patrick C. Alguire, MD, FACP
American College of Physicians
Philadelphia, Pennsylvania

Deputy Editor

Janet A. Jokela, MD, MPH, FACP
Professor & Head, Department of Medicine
Acting Regional Dean
University of Illinois College of Medicine
Urbana, Illinois

Pulmonary and Critical Care Medicine Reviewers

Hugh Cassiere, MD, FACP
Janaki Deepak, MBBS, FACP
Joel Deitz, MD
Glenn Eiger, MD, FACP
David Hostler, MD, MPH, FACP
Jordanna Mae Hostler, MD, FACP
William R. Hunt, MD, FACP
Marshaleen N. Henriques King, MD, MSc, FACP
Laura Meinke, MD, FACP
Bhupinder Natt, MD, FACP
Jody C. Olson, MD, FACP
Iqbal Ratnani, MD
Alexander Sy, MD, MBA, FACP
Tammy Wichman, MD, FACP

Pulmonary and Critical Care Medicine ACP Editorial Staff

Sandy Crump, Medical Editor, Assessment and Education Programs

Becky Krumm, Director, Assessment and Education Programs

Jackie Twomey, Managing Editor, Assessment and Education Programs

ACP Principal Staff

Davoren Chick, MD, FACP
Senior Vice President, Medical Education

Tabassum Salam, MD, MBA, FACP
Vice President, Medical Education

Margaret Wells, EdM
Vice President, Learning Assessment, Accreditation, and Research

Patrick C. Alguire, MD, FACP
MKSAP Senior Deputy Editor

Becky Krumm
Director, Assessment and Education Programs

Jackie Twomey
Managing Editor

Julia Nawrocki
Digital Content Associate/Editor

Linnea Donnarumma
Senior Medical Editor

Amanda Cowley
Medical Editor

Sandy Crump
Medical Editor

Georgette Forgione
Medical Editor

Beth Goldner
Medical Editor

Suzanne Meyers
Medical Editor

Elise Paxson
Medical Editor

Chuck Graver
Finance and Operations Administrator

Kimberly Kerns
Administrative Coordinator

Disclosures of relationships with any entity producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients. Individuals not listed below have nothing to disclose.

Neal Chaisson, MD
Consultantship
Actelion, Bayer
Speakers Bureau
Gilead, Bayer, United Therapeutics
Other
Putnam Associates, Schlesinger Associates

Eduardo Mireles-Cabodevila, MD
Patent Holder
Cleveland Clinic

Tabassum Salam, MD, MBA, FACP
Consultantship
Johnson & Johnson

Acknowledgments

The American College of Physicians (ACP) gratefully acknowledges the special contributions to the development and production of the 19th edition of the Medical Knowledge Self-Assessment Program® (MKSAP® 19) made by the following people:

Graphic Design: Barry Moshinski (Director, Graphic Services), Raymond DeJohn (Designer, Graphic Services), Tom Malone (Print/Mail Production Manager, Graphic Services), Mike Ripca (Technical Administrator, Graphic Services).

Production/Systems: Dan Hoffmann (Vice President, Information Technology), Scott Hurd (Manager, Content Systems), Neil Kohl (Senior Architect), and Chris Patterson (Senior Architect).

MKSAP 19 Digital: Under the leadership of Steven Spadt (Senior Vice President, Information Technology and Chief Technology Officer), the development of the digital version of MKSAP 19 was implemented by ACP's Digital Products and Services Department, directed and led by Brian Sweigard (Vice President, Digital Products and Services). Other members of the team included Dan Barron (Senior Web Application Developer/Architect), Callie Cramer (Data Visualization/Web Developer), Chris Forrest (Senior Web Application Developer), Kathleen Hoover (Manager, User Interface Design and Development), Kara Regis (Director, Product Design and Development), Brad Lord (Senior Web Application Developer/Architect), and John McKnight (Senior Web Developer).

The College also wishes to acknowledge that many other persons, too numerous to mention, have contributed to the production of this program. Without their dedicated efforts, this program would not have been possible.

MKSAP Resource Page

The MKSAP Resource Page (www.acponline.org/mksap19-resources) provides access to MKSAP 19 online answer sheets for transcribing answers from the print edition; access to MKSAP 19 Digital; Board Basics®; information on Continuing Medical Education (CME), Maintenance of Certification (MOC), and international Continuing Professional Development (CPD) and MOC; errata; and other new information.

International MOC/CPD

Information and instructions on submission of international MOC/CPD is available by accessing the CME/MOC/CPD tab on the left navigation menu of MKSAP 19 Digital.

Continuing Medical Education

The American College of Physicians is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American College of Physicians designates this enduring material, MKSAP 19, for a maximum of 300 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Up to 25.75 *AMA PRA Category 1 Credits*™ are available from January 31, 2022, to January 31, 2025, for the MKSAP 19 Pulmonary and Critical Care Medicine section.

Learning Objectives

The learning objectives of MKSAP 19 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve clinical management decisions that affect patient safety and quality of care
- Determine when to refer patients for care by medical subspecialists, surgeons, and other members of the health care team
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internal medicine specialists, including primary care physicians and hospitalists
- Internal medicine subspecialists who desire to remain up to date in internal medicine
- Residents preparing for the ABIM Internal Medicine Certification Examination
- Physicians engaged in the ABIM Maintenance of Certification Longitudinal Assessment Option, preparing for the ABIM Internal Medicine Maintenance of Certification Examination, or engaged with the ABIM Focused Practice in Hospital Medicine program

Earn CME Credits or MOC Points Online

To earn CME credits or to apply for MOC points, MKSAP users need to answer at least one of two questions correctly (earning a score of at least 50%) and click the Submit CME button. Each single MKSAP 19 self-assessment question qualifies for one quarter of a CME credit hour or ABIM MOC point.

MKSAP 19 Subscribers can enter their self-assessment question answers and submit for CME/MOC in two ways:

1. Users of MKSAP 19 Complete who prefer to use their print books and a paper answer sheet to study and record their answers can use the printed answer sheet at the back of this book to record their answers. The corresponding online answer sheets, which are available on the MKSAP 19 Resource Page, may be used to transcribe answers onto the online answer sheets. Users may then submit their answers to qualify for CME credits or MOC points (see below for information on Opting in for MOC). Users who prefer to record their answers on a paper answer sheet should save their answer sheet for future use. Users who study with MKSAP 19 print can also submit their answers directly within MKSAP 19 Digital by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions.

2. Users of MKSAP 19 Digital can enter their answers within the digital program by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions and clicking the Submit CME button once they qualify for CME and are ready to submit. Learners should keep in mind their yearly CME and MOC deadlines when determining the appropriate time to submit.

Learners' CME/MOC submission progress will be shown on the MKSAP 19 Digital CME/MOC/CPD page.

Opting in for MOC

MKSAP 19 users can opt in for simultaneous submission of CME and MOC points as they answer self-assessment questions. To opt in, users will be required to complete a form requesting their name, date of birth, and ABIM number. The MOC Opt-in Form will be presented during a user's first CME submission and needs to be completed only once.

ABIM Maintenance of Certification

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 300 medical knowledge MOC points in the ABIM's MOC program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

Disclosure Policy

It is the policy of the American College of Physicians (ACP) to ensure balance, independence, objectivity, and scientific rigor in all of its educational activities. To this end, and consistent with the policies of the ACP and the Accreditation Council for Continuing Medical Education (ACCME), contributors to all ACP continuing medical education activities are required to disclose all relevant financial relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. Contributors are required to use generic names in the discussion of therapeutic options and are required to identify any unapproved, off-label, or investigative use of commercial products or devices. Where a trade name is used, all available trade names for the same product type are also included. If trade-name products manufactured by companies with whom contributors have relationships are discussed, contributors are asked to provide evidence-based citations in support of the discussion. The information is reviewed by the committee responsible for producing this content. If necessary, adjustments to topics or contributors' roles in content development are made to balance the discussion. All relevant relationships are mitigated. Readers of this content are asked to evaluate it for evidence of commercial bias and send any relevant comments to mksap_editors@acponline.org so that future decisions about content and contributors can be made in light of this information.

Mitigation of Conflicts

To mitigate all conflicts of interest and influences of vested interests, ACP's content planners used best evidence and updated clinical care guidelines in developing content, when such evidence and guidelines were available. All content underwent review by external peer reviewers not on the committee to ensure that the material was balanced and unbiased. Contributors' disclosure information can be found with the list of contributors' names and those of ACP principal staff listed in the beginning of this book.

Language Reflecting Diversity, Equity, and Inclusion Within MKSAP 19

MKSAP 19's Editors and contributors commit to using language and images that support ACP's commitment to being an anti-racist organization that supports diversity, equity, and inclusion throughout health care and health education. ACP also continues to ensure diversity among MKSAP's physician-contributors. When appropriate, the MKSAP Editors will also rely on MKSAP 19 Digital's expanded use of multimedia enhancements, including video and audio, to explore and more fully explain issues surrounding the presentation of MKSAP 19 clinical content as it relates to race and ethnicity. MKSAP 19 users are encouraged to contact the Editors at mksap_editors@acponline.org to help us identify opportunities for improvement in this area.

Hospital-Based Medicine

For the convenience of subscribers who provide care in hospital settings, comprehensive hospital-focused content aligned with the ABIM Focused Practice in Hospital Medicine blueprint is integrated throughout the syllabus, and self-assessment questions that are specific to the hospital setting are specially designated with the blue hospitalist icon (H).

High Value Care Key Points

Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon [**HVC**].

Educational Disclaimer

The editors and publisher of MKSAP 19 recognize that the development of new material offers many opportunities for error. Despite our best efforts, some errors may persist in print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to ensure that the recommended dosages in MKSAP 19 concur with the information provided in the product information material. This is especially important in cases of new, infrequently used, or highly toxic drugs. Application of the information in MKSAP 19 remains the professional responsibility of the practitioner.

The primary purpose of MKSAP 19 is educational. Information presented, as well as publications, technologies, products, and/or services discussed, is intended to inform subscribers about the knowledge, techniques, and experiences of the contributors. A diversity of professional opinion exists, and the views of the contributors are their own and not those of the ACP. Inclusion of any material in the program does not constitute endorsement or recommendation by the ACP. The ACP does not warrant the safety, reliability, accuracy, completeness, or usefulness of and disclaims any and all liability for damages and claims that may result from the use of information, publications, technologies, products, and/or services discussed in this program.

Publisher's Information

Copyright © 2022 American College of Physicians. All rights reserved.

This publication is protected by copyright. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic or mechanical, including photocopy, without the express consent of the ACP. MKSAP 19 is for individual use only. Only one account per subscription will be permitted for the purpose of earning CME credits and MOC points and for other authorized uses of MKSAP 19.

Disclaimer Regarding Direct Purchases from Online Retailers

CME and/or MOC for MKSAP 19 is available only to customers who purchase the program directly from ACP. ACP will not set up MKSAP CME/MOC accounts for purchasers of MKSAP sold by unauthorized sellers (e.g., Amazon, eBay), with whom ACP has no relationship. We do not honor third party sales. CME credits and MOC points cannot be awarded to those purchasers who have purchased the program from non-authorized sellers.

Unauthorized Use of This Book Is Against the Law

Unauthorized reproduction of this publication is unlawful. ACP prohibits reproduction of this publication or any of its parts in any form either for individual use or for distribution.

ACP will consider granting an individual permission to reproduce only limited portions of this publication for his or her own exclusive use. Send requests in writing to MKSAP® Permissions, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106-1572, or email your request to mksap_editors@acponline.org.

MKSAP 19 ISBN: 978-1-938245-75-6
Pulmonary and Critical Care Medicine ISBN: 978-1-938245-86-2

Printed in the United States of America.

For order information in the U.S. or Canada, call 800-ACP-1915. In all other countries, call 215-351-2600 (Monday to Friday, 9 AM–5 PM ET). Fax inquiries to 215-351-2799 or email to custserv@acponline.org.

Errata and Revisions

Errata and Revisions for MKSAP 19 will be available through MKSAP 19 Digital at mksap19.acponline.org as new information becomes known to the editors.

Table of Contents

Pulmonary Diagnostic Tests

- Pulmonary Function Testing . . . 1
  - Spirometry . . . 1
  - Bronchial Challenge Testing . . . 1
  - Lung Volumes and DLCO . . . 1
  - Pulmonary Function Testing Interpretation . . . 1
  - 6-Minute Walk Test . . . 2
  - Pulse Oximetry . . . 3
  - Fractional Exhaled Nitric Oxide . . . 3
- Imaging and Bronchoscopy . . . 3
  - Imaging . . . 3
  - Bronchoscopy and Endobronchial Ultrasonography . . . 5

Airways Disease

- Asthma . . . 5
  - Epidemiology and Natural History . . . 5
  - Pathogenesis . . . 7
  - Risk Factors . . . 7
  - Symptoms and Clinical Evaluation . . . 7
  - Asthma Syndromes . . . 8
  - Management of Chronic Asthma . . . 9
  - Management of Asthma Exacerbations . . . 14
  - Severe Refractory Asthma . . . 14
  - Asthma in Pregnancy . . . 15
- Chronic Obstructive Pulmonary Disease . . . 15
  - Definition . . . 15
  - Epidemiology . . . 15
  - Pathophysiology . . . 15
  - Risk Factors . . . 15
  - Heterogeneity of COPD . . . 15
  - Comorbid Conditions . . . 16
  - Diagnosis . . . 16
  - Disease Assessment . . . 16
  - Management of COPD . . . 17
  - Acute Exacerbations . . . 21
- Bronchiectasis . . . 22
  - Definition . . . 22
  - Causes . . . 22
  - Presentation . . . 22
  - Diagnosis . . . 23
  - Treatment . . . 23
- Cystic Fibrosis . . . 24
  - Diagnosis . . . 24
  - Treatment . . . 24

Diffuse Parenchymal Lung Disease

- Classification and Epidemiology . . . 25
- Diagnostic Approach and Evaluation . . . 25
  - High-Resolution CT Scanning . . . 26
  - Serologic Testing . . . 27
  - Lung Biopsy . . . 27
- Diffuse Parenchymal Lung Diseases With a Known Cause . . . 27
  - Smoking-Related Diffuse Parenchymal Lung Disease . . . 27
  - Connective Tissue Diseases . . . 27
  - Hypersensitivity Pneumonitis . . . 27
  - Drug-Induced Diffuse Parenchymal Lung Disease . . . 28
  - Radiation Pneumonitis . . . 28
- Diffuse Parenchymal Lung Diseases With an Unknown Cause . . . 30
  - Idiopathic Pulmonary Fibrosis . . . 30
  - Nonspecific Interstitial Pneumonia . . . 30
  - Cryptogenic Organizing Pneumonia . . . 31
  - Acute Interstitial Pneumonia . . . 31
  - Combined Pulmonary Fibrosis and Emphysema . . . 31
- Sarcoidosis . . . 31

Occupational Lung Disease

- When to Suspect an Occupational Lung Disease . . . 33
- Key Elements of the Exposure History . . . 33
- Management . . . 34
- Surveillance . . . 35

Pleural Disease

- Pleural Effusion . . . 35
  - Evaluation . . . 35
  - Management . . . 39
- Pneumothorax . . . 40
  - Evaluation . . . 40
  - Management . . . 40

Pulmonary Vascular Disease

- Pulmonary Hypertension . . . 41
  - Evaluation of Suspected Pulmonary Hypertension . . . 41
- Pulmonary Arterial Hypertension (Group 1) . . . 41
  - Diagnosis . . . 43
  - Management . . . 43

Chronic Thromboembolic Pulmonary Hypertension (Group 4) 44
    Diagnosis 44
    Management 45
Other Types of Pulmonary Hypertension (Groups 2, 3, and 5) 45
    Diagnosis 45

Lung Tumors

Pulmonary Nodule Evaluation 45
    Solid Indeterminate Nodule Larger Than 8 mm . . . 46
    Solid Indeterminate Nodule of 8 mm or Smaller . . . 46
    Subsolid Nodule 46
Lung Cancer 47
    Lung Cancer Types 47
    Risk Factors 48
    Screening 48
    Diagnosis and Staging 49
    Other Pulmonary Neoplasms 49
    Mesothelioma 50
Mediastinal Masses 50
    Anterior Mediastinum 50
    Middle Mediastinum 51
    Posterior Mediastinum 51

Sleep Medicine

Excessive Daytime Sleepiness 51
Conditions that Disrupt Circadian Rhythm 52
    Jet Lag 52
    Shift Work Sleep Disorder 52
Obstructive Sleep Apnea 52
    Pathophysiology 52
    Risk Factors 53
    Clinical Features and Diagnosis 53
    Treatment 53
Central Sleep Apnea Syndromes 54
    Classification and Pathophysiology 54
    Risk Factors 54
    Symptoms and Diagnosis 55
    Treatment 55
Sleep-Related Hypoventilation Syndromes 55
    Chronic Obstructive Pulmonary Disease 55
    Obesity Hypoventilation Syndrome 55
    Neuromuscular Diseases 56

High-Altitude–Related Illnesses

Pathogenesis of High-Altitude Illness 56
Acute Mountain Sickness 56
High-Altitude Cerebral Edema 57
High-Altitude Pulmonary Edema 57
Air Travel in Pulmonary Disease 57

Critical Care Medicine: ICU Utilization

Recognizing the Critically Ill Patient 58
Organization of Critical Care 58

Principles of Critical Care

Comprehensive Support of Critically Ill Patients 59
    Sedation and Analgesia 59
    Nutritional Support 60
    Early Mobilization 61
    ICU Care Bundles 61
    High Value Care in the ICU 61
    Respiratory Support 61
    Mechanical Ventilatory Support: General Principles 62
    Hemodynamic Support 63
    Intravenous Access 63
    Blood Pressure Support 65
ICU Complications 66
    ICU-Acquired Weakness 66
    Long-Term Cognitive Impairment 66
    Post—Intensive Care Syndrome 67

Common ICU Conditions

Acute Respiratory Failure 67
    Acute Upper Airway Management 67
    Hypoxemic Respiratory Failure 68
    Acute Inhalational Injuries 68
    Acute Respiratory Distress Syndrome 69
    Heart Failure 70
    Atelectasis 71
    Pneumonia 71
    Diffuse Parenchymal Lung Disease 71
    Pulmonary Embolism 72
    Hypercapnic (Ventilatory) Respiratory Failure 72
Shock 75
    Distributive Shock 76
    Hypovolemic Shock 76
    Cardiogenic Shock 76
    Obstructive Shock 77
Sepsis 77
    Definition, Pathophysiology, and Clinical Presentation of Sepsis 77
    Epidemiology of Sepsis 78
    Management of Sepsis 78

Specific Critical Care Topics

Anaphylaxis 80
Hyperthermic Emergencies 81
    Heat Stroke 81
    Malignant Hyperthermia 81

Neuroleptic Malignant Syndrome and Serotonin Syndrome . . . 82
Accidental Hypothermia . . . 82
Toxicology . . . 82
Alcohol Poisoning . . . 82
Carbon Monoxide Poisoning . . . 83
Cyanide Poisoning . . . 84
Toxicity of Drugs of Abuse . . . 85
Overdose of Therapeutic Drugs . . . 86
Acute Abdominal Surgical Emergencies . . . 86
Fat Embolism . . . 87
Approach to the Critically Ill Patient Who Is Pregnant . . . 87
Encephalopathy . . . 87
Coma . . . 87
Anoxic Brain Injury . . . 88

Bibliography . . . 89

Self-Assessment Test . . . 93

Index . . . 175

Pulmonary and Critical Care Medicine High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 19 in several important ways. MKSAP 19 includes HVC-identified key points in the text, HVC-focused multiple-choice questions, and, in MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Pulmonary and Critical Care Medicine section of MKSAP 19.

- A key clinical indicator of occupational asthma is symptom improvement during weekends and time away from work; spirometry before and after workplace exposures is a cost-effective way to confirm a suspected diagnosis of occupational asthma.
- Fractional exhaled nitric oxide measurement (FeNO) is not recommended to guide asthma treatment in the general population (see Item 85).
- Administration of a glucocorticoid and a long-acting β_2-agonist in a single inhaler is preferred because it improves adherence and may reduce cost compared with administration of each drug in a separate inhaler (see Item 13).
- In patients with COPD exacerbation, short courses of lower-dose oral glucocorticoids (prednisone 40 mg/d for 5 days) have been found to be equivalent to higher doses, longer courses, and intravenous administration (see Item 64).
- A sputum culture is not routinely used to assess COPD exacerbations, as it rarely affects management.
- Patients not using baseline oxygen and with a resting SpO_2 of less than 92% should be prescribed supplemental oxygen during air travel without additional testing (see Item 82).
- When high-resolution CT findings are classic for usual interstitial pneumonia, lung biopsy is not necessary for diagnosis.
- The diagnosis of cryptogenic organizing pneumonia (COP) may not require lung biopsy if the clinical presentation and high-resolution CT findings are consistent with COP.
- In patients with radiographic evidence of advanced-stage lung cancer, diagnosis and staging are best accomplished with a single invasive test at a location that will establish both the diagnosis and the stage of disease.
- Benzodiazepines should not be used for treating delirium unless they are needed to treat alcohol withdrawal or seizures.
- In patients receiving enteral feedings, routine measurement of gastric residuals is not recommended because it delays achievement of feeding goals, increases the risk of clogging the enteral access, and may increase the risk for aspiration.
- Administration of parenteral nutrition to supplement enteral nutrition may lead to harm and should be avoided.
- Bronchoscopy for airway mucous clearance to prevent postoperative atelectasis offers no clear benefit compared with other methods of chest physiotherapy.
- Evidence for pulmonary artery catheters demonstrates a lack of benefit and, in some cases, increased risk to patients.
- Given the relative expense of colloids, crystalloid administration is generally preferred and recommended by guidelines in the treatment of septic shock.
- There is no role for glucocorticoids in sepsis without shock.
- Clinical presentations of sarcoidosis that do not require a biopsy include asymptomatic stage I pulmonary sarcoidosis, Löfgren syndrome, and Heerfordt syndrome (see Item 16).
- Providing supplemental oxygen in acutely ill medical patients with normal oxygen saturation increases mortality

in a dose-dependent manner and is not recommended (see Item 45).

- Approximately 20% of laboratory tests obtained in hospitalized patients are not needed (see Item 76).
- Excessive laboratory testing in hospitalized patients can result in iatrogenic anemia (see Item 76).
- Discontinuing antibiotic therapy is appropriate in patients who initially were thought to have sepsis but do not (see Item 96).
- In older persons with nonexertional hyperthermia, ice water immersion is associated with increased mortality and should not be used (see Item 4).
- In patients with portal hypertension and acute gastrointestinal bleeding, transfusion to 10 g/dL (100 g/L) or higher can rapidly increase portal pressure, putting the patient at significant risk for rebleeding and is not recommended (see Item 53).

Pulmonary and Critical Care Medicine

Pulmonary Diagnostic Tests

Pulmonary Function Testing

Pulmonary function testing can include spirometry, response to bronchodilators, bronchial challenge testing, lung volume testing, and measurement of DLCO. These findings are compared with age, sex, height, and race-adjusted population norms and are expressed as a percentage of the predicted value (**Table 1**). The 2005 American Thoracic Society guidelines define the lower limit of normal as below the fifth percentile of the predicted value; some laboratories use this as their cutoff, and typically this coincides with 80% of the predicted value.

KEY POINT

- In general, pulmonary function test results below 80% of predicted indicate pulmonary impairment.

Spirometry

Spirometry measures the maximal volume and flow of air during a best-effort forced exhalation; reported values include FEV_1, FVC, and the FEV_1/FVC ratio. Spirometry correlates with home peak expiratory flow meter measurements but is more reliable, provides more data, and is used in diagnosis and management of airways disease. Although spirometry is easily performed in the outpatient setting, technical test validation and patient factors, including poor effort, coughing, and failure to exhale for a minimum of 6 seconds, may result in suboptimal test performance and misinterpretation. If spirometry is unable to be performed, fractional exhaled nitric oxide measurement may help in the diagnosis of asthma (see following section).

TABLE 1. Characterization of Impairment Severity in Pulmonary Function Tests

Severity of Impairment	% of Predicted
FEV_1	
Mild	70-79
Moderate	60-69
Moderately severe	50-59
Severe	35-49
Very severe	<35
DLCO	
Mild	<LLN but >60
Moderate	40-60
Severe	<40

LLN = lower limit of normal; below the fifth percentile of healthy never-smokers.

Reproduced with permission of the © ERS 2021, from Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:957. [PMID: 16264058].

Bronchial Challenge Testing

Bronchial challenge testing is used to identify bronchial hyperresponsiveness. This is particularly helpful in patients whose symptoms suggest asthma but for whom other pulmonary function test results are normal. Patients inhale increasing doses of a substance known to induce bronchospasm, such as methacholine or histamine, in a stepwise fashion. This is followed by repeated measurement of FEV_1; the test is considered positive if FEV_1 falls by 20% or more from the baseline value. Bronchial challenge testing has a high negative predictive value for ruling out asthma. However, a positive test can be caused by other conditions, including COPD, smoking, upper respiratory infections, allergic rhinitis, bronchiectasis, and cystic fibrosis.

KEY POINT

- Bronchial challenge testing is a helpful diagnostic tool to use for patients whose symptoms suggest asthma but for whom other pulmonary function test results are normal. **HVC**

Lung Volumes and DLCO

Lung volumes can be measured by body plethysmography of nitrogen diffusion. Measures include total lung capacity (TLC), vital capacity, functional residual capacity, expiratory reserve volume, and residual volume. DLCO measurement estimates the amount of gas transfer through the alveolar-capillary unit and is proportional to the surface area of functional lung. DLCO is measured by inhalation of a gas mixture containing carbon monoxide and helium; the resulting value is corrected for hemoglobin level.

Pulmonary Function Testing Interpretation

The purpose of pulmonary function testing interpretation is to classify abnormal results as obstructive, restrictive, or mixed obstructive/restrictive and to assess the severity of impairment (**Figure 1**). A reduced FEV_1/FVC ratio is consistent with obstruction, and the severity of obstruction is determined according to the measured FEV_1 as a percentage of the predicted value (see Table 1). The American Thoracic Society and

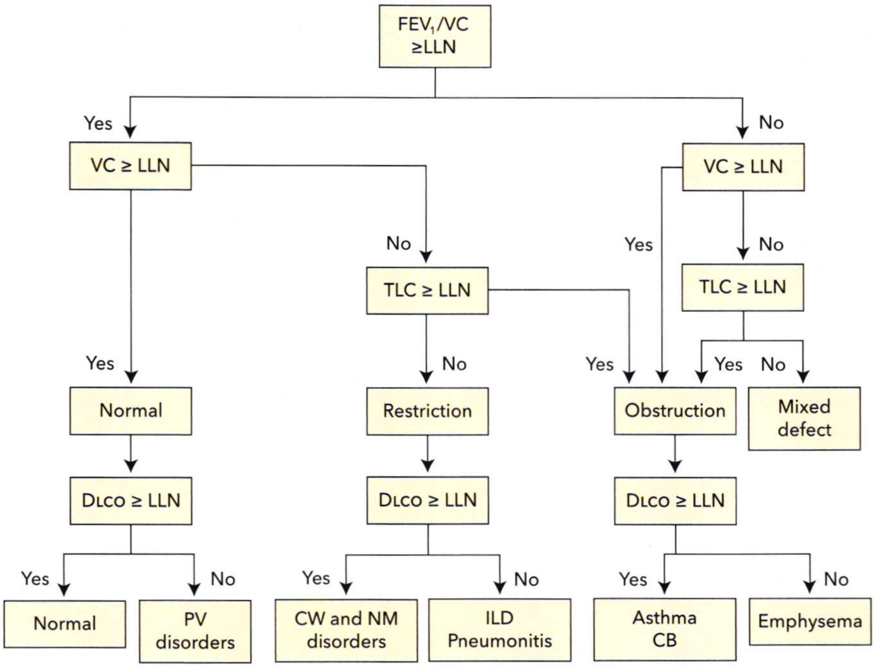


FIGURE 1. A simplified algorithm such as this may be used to assess lung function in clinical practice. It presents classic patterns for various pulmonary disorders. As in any such diagram, patients may or may not present with the classic patterns, depending on their illnesses, severity, and lung function before disease onset (for example, did they start with a vital capacity [VC] close to the upper or lower limit of normal [LLN]?). The decisions about how far to follow this diagram are clinical and will vary depending on the questions being asked and the clinical information available at the time of testing. The FEV$_1$/VC ratio and VC should be considered first. Total lung capacity (TLC) is necessary to confirm or exclude the presence of a restrictive defect when VC is below the LLN. The algorithm also includes DLCO measurement with the predicted value adjusted for hemoglobin. In the mixed-defect group, the DLCO patterns are the same as those for restriction and obstruction. This flow chart is not suitable for assessing the severity of upper airway obstruction. CB = chronic bronchitis; CW = chest wall; ILD = interstitial lung diseases; NM = neuromuscular; PV = pulmonary vascular.

Reproduced with the permission of the © ERS 2021, from Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948-68. [PMID: 16264058]

the European Respiratory Society define a reduced FEV$_1$/FVC ratio as being below the lower limit of normal, whereas the Global Initiative for Chronic Obstructive Lung Disease defines it as below 0.70. An increase from baseline in FEV$_1$, FVC, or both of at least 12% and at least 200 mL indicates a positive bronchodilator response (reversibility). TLC is normal or even increased in pure obstructive disease. Elevation of TLC and residual volume (120% or greater of predicted) can be observed in obstruction and generally indicates hyperinflation and air trapping, a common pattern in severe COPD and asthma.

If FEV$_1$ or FVC is reduced and the FEV$_1$/FVC ratio is 0.70 or greater, then the pattern may be interpreted as restrictive, but measurement of TLC is needed to confirm this. If TLC is less than 80% of predicted (or the lower limit of normal), a restrictive pattern is present.

Some patients present with coexisting obstructive and restrictive pulmonary disorders, such as COPD and interstitial lung disease. In these cases, a low FEV$_1$/FVC ratio (obstructive) and a low TLC (restrictive) are both present.

DLCO is reduced in conditions in which functioning alveolar-capillary units are destroyed (COPD), infiltrated (interstitial lung diseases), or removed (lung resection), and in which their function is compromised (pulmonary parenchymal and vascular disorders). Conditions that increase pulmonary capillary blood volume, such as pulmonary alveolar hemorrhage, left-to-right shunt, or asthma, can cause an elevation in DLCO.

The flow-volume loop is a graphic representation of maximally forced inspiratory and expiratory flow (on the Y-axis) against volume (on the X-axis). The shape of the spirometric flow-volume loop is also useful in differentiating obstructive from restrictive patterns (**Figure 2**).

KEY POINTS

- The purpose of pulmonary function testing interpretation is to classify abnormal results as either obstructive or restrictive and to assess the severity of impairment.
- The FEV$_1$/FVC ratio is the primary measurement that defines obstructive disease, and total lung capacity is the primary measurement used to confirm restrictive disease.

6-Minute Walk Test

The 6-minute walk test provides a valid and reliable measurement of exercise capacity in patients with lung disease. Patients walk at their own pace along a course for 6 minutes, and the total distance walked is recorded. Lower 6-minute walk test distances correlate with increased mortality in several lung diseases, including COPD, interstitial lung disease, and pulmonary arterial hypertension. Serial 6-minute walk testing may be used to assess response to therapy in patients with chronic respiratory disorders, especially pulmonary arterial hypertension.

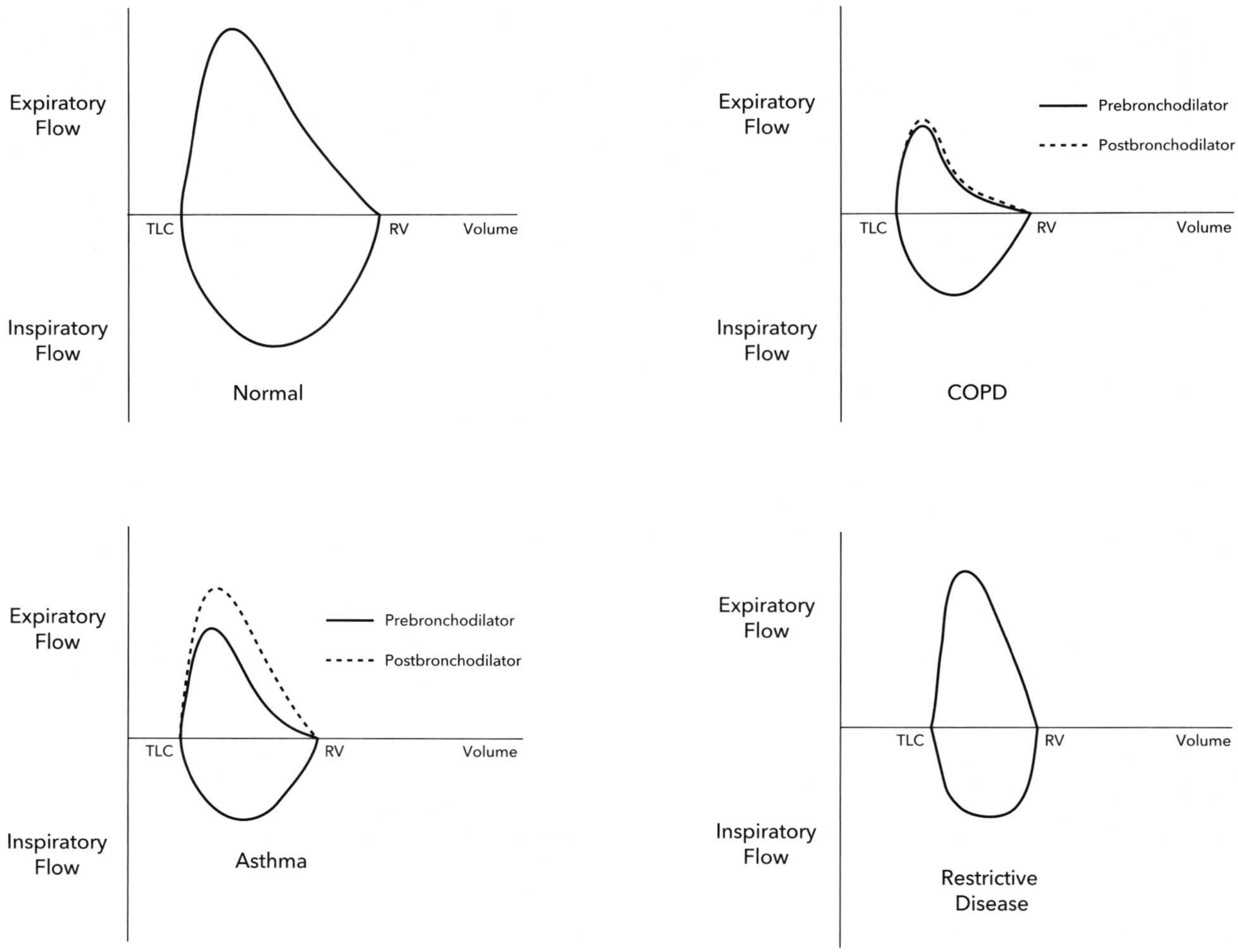


FIGURE 2. Pulmonary function test flow-volume patterns. RV = residual volume; TLC = total lung capacity.

Pulse Oximetry

Oximeters work by calculating the difference between absorption of infrared light by oxygenated and deoxygenated blood. A normal hemoglobin saturation measured by pulse oximetry is 95% to 100%, and values below 90% indicate hypoxemia. Substances in the blood that absorb infrared light may cause erroneous readings, including carboxyhemoglobin (present in carbon monoxide poisoning), methemoglobin (caused by nitrates), methylene blue, and some topical anesthetics. More commonly, patient factors such as cool extremities, poor circulation, nail polish, and motion artifact result in erroneous readings. In these cases, alternative methods of measuring oxygenation, such as arterial blood gas analysis, are needed.

Fractional Exhaled Nitric Oxide

Measurement of the fraction of nitric oxide in an exhaled breath sample (FeNO) provides a noninvasive way to quantify eosinophilic airway inflammation and serves as a complementary tool in the management of lung diseases—asthma in particular. Elevated FeNO levels correlate modestly with blood and sputum eosinophilia. More than half of patients with asthma have eosinophilic (type 2) airway inflammation, and FeNO levels may help predict glucocorticoid responsiveness in these patients as well as monitor their response to and adherence to anti-inflammatory therapy. The American Thoracic Society guidelines suggest that FeNO levels above 50 ppb indicate glucocorticoid-sensitive airway inflammation. Patients with levels below 25 ppb are less likely to have eosinophilic inflammation and glucocorticoid responsiveness. Fractional exhaled nitric oxide testing is recommended as an adjunct in asthma evaluation for those aged 5 years and older. Specific recommendations for the use of nitric oxide testing include when the diagnosis of asthma is uncertain after standard evaluation or when spirometry cannot be performed (conditional recommendation) and in persistent allergic asthma and uncertainty in choosing, monitoring, or adjusting medications (conditional recommendation).

Imaging and Bronchoscopy

Imaging

Table 2 provides information on various imaging modalities and their indications.

TABLE 2. Pulmonary Imaging Modalities and Indications

Modality	Indications	Common Conditions/Uses	Advantages	Disadvantages	Relative Radiation Level
Chest radiography	Initial imaging for most pulmonary patients	Acute respiratory illness Pneumothorax Dyspnea Heart failure Chest pain	Widely available Portable Suitable for critically ill patients	Low resolution Two-dimensional imaging	Low
Chest CT	Evaluate abnormality seen on chest radiograph Examine parenchymal architecture Evaluate mediastinal structures Visualize small lesions not seen on chest radiograph Angiography of pulmonary vessels	Malignancies Interstitial lung disease Suspected pulmonary embolism Lung nodules Lung cancer screening Hemoptysis Complicated acute respiratory illness Blunt chest trauma	High resolution Provides detail of lung anatomy	Requires patient transportation and cooperation Risks with use of intravenous contrast (kidney toxicity, anaphylaxis)	High
Ultrasonography	Evaluate acute dyspnea Characterize pleural space and diaphragm	Pleural effusion Heart failure Pneumothorax Diaphragm function Thoracentesis Tube thoracostomy	Portable Real-time assessment Suitable for critically ill patients	Lower resolution Image acquisition is operator and patient dependent	None
PET/CT	Assess metabolic tissue activity	Malignancy staging Biopsy localization	Allows correlation of anatomy with physiologic activity	Requires patient transportation and cooperation	High

Chest Radiography

Conventional chest radiographs are indicated as the initial imaging procedure for most patients with significant respiratory symptoms. Posteroanterior and lateral views should be obtained. The advantages are the availability of testing and the low dose of radiation exposure for the patient. The limitations include the need to take a deep inspiration, breath holding, image resolution, and the two-dimensional images produced.

Computed Tomography

CT of the thorax allows detailed, high-resolution imaging of the lungs and options for both static and dynamic imaging techniques. Helical scanners allow rapid scanning but may require patients to hold their breath at full inspiration for 30 seconds or more. Reconstruction can include sagittal and coronal images, which result in three-dimensional representation of the extent and distribution of disease. More specialized techniques reformat the data to highlight specific structures; they include maximum intensity projection, which focuses on the vasculature, and minimum intensity projection, which focuses on the airways. Additional variables in CT imaging include slice thickness and interval. Contrast enhancement may be used to augment the value of imaging on the basis of the underlying disease.

The choice of examination depends on the clinical context and information sought. Noncontrast CT is usually preferred because contrast makes assessing the lung parenchyma more difficult. For most patients, routine (slice thickness of 2 or 2.5 mm) noncontrast CT provides the needed information. For patients suspected of having interstitial lung disease, a high-resolution (slice thickness of 1 mm) study should be ordered. Additional expiratory views can evaluate for air trapping and further inform the diagnosis of small airways disease. However, because the slice interval (the distance between individual slices) with high-resolution CT is larger than with conventional CT, this technique "skips" interval sections of the lung and should not be used to evaluate lung nodules. Use of intravenous contrast dye helps delineate mediastinal structures and is particularly useful in patients with suspected lymphadenopathy or vascular pathology. CT angiography is used for detection of pulmonary embolism and uses a rapid, timed bolus of intravenous contrast.

CT scanning exposes the patient to a much higher dose of radiation than traditional chest radiographs, and CT is currently the primary source of imaging radiation exposure for patients. Low-dose CT scanning is now the recommended choice for lung cancer screening in the United States (see Lung Tumors).

KEY POINT

- High-resolution CT techniques are preferred for evaluation of interstitial lung disease; conventional noncontrast CT is used to evaluate lung nodules and most other lung disease; and CT angiography is used for detection of pulmonary embolism.

Ultrasonography of the Lung and Diaphragm

Point-of-care thoracic ultrasonography provides a noninvasive means of rapidly assessing the lungs, pleura, and diaphragm. It is particularly helpful for critically ill patients for whom the use of other imaging techniques requiring transport may pose undue risk or delay diagnosis. Thoracic ultrasonography detects the presence and volume of pleural effusions more accurately than chest radiography; it can also identify characteristics that suggest an effusion and difficulty or risks with draining the effusion. In addition, performing pleural drainage procedures such as thoracentesis or tube thoracostomy with ultrasound guidance reduces risks for complications, including pneumothorax. Thoracic ultrasonography assesses diaphragm function more accurately than fluoroscopy. Ultrasonography of the lung parenchyma can identify consolidation, whereas demonstration of movement of the visceral pleura against the parietal pleura (lung sliding sign) excludes a pneumothorax at the area scanned. Obesity and significant edema or musculature can degrade image quality and limit ultrasound usefulness, whereas complex or high-density pleural collections (empyema, hemothorax) may be too echogenic for accurate detection or identification of adjacent tissue structures.

Positron Emission Tomography

PET uses the radionuclide 18-fluoro-2-deoxyglucose, which accumulates within highly metabolically active cells such as cancer cells and can be visualized as discrete areas of uptake. Integrated PET/CT allows improved localization of the metabolic activity. PET scans are widely used to evaluate the likelihood of malignancy in lung nodules, to stage known thoracic tumors, and to evaluate for metastatic disease from other nonthoracic malignancies. False-positive PET scans can occur in other hypermetabolic conditions in which cells accumulate fluorodeoxyglucose, such as infection or inflammation. False negatives can occur when tumors have low rates of metabolic activity, such as carcinoid, adenocarcinoma in situ, and rarely, metastatic kidney, prostate, or testicular cancer. PET is not useful for the determination of malignant potential in lung nodules less than 8 mm in size.

Bronchoscopy and Endobronchial Ultrasonography

Bronchoscopy is a diagnostic (**Table 3**) and therapeutic (**Table 4**) tool for patients with lung disorders. It is used for the diagnosis of localized and diffuse pulmonary diseases and is important in the diagnostic evaluation of pulmonary infections, particularly in the immunocompromised host, as well as for various therapeutic uses. Endobronchial ultrasonography is the initial procedure of choice for obtaining tissue from mediastinal and hilar lymph nodes in the diagnosis and staging of patients with known or suspected thoracic malignancy.

KEY POINT

- Endobronchial ultrasonography is the initial procedure of choice for obtaining tissue from mediastinal and hilar lymph nodes in the staging of patients with known or suspected thoracic malignancy.

Airways Disease

Asthma

Epidemiology and Natural History

Asthma is an inflammatory disorder of the airways characterized by cough, wheezing, chest tightness, dyspnea, and variable airflow obstruction. Asthma is a major health burden throughout the world; approximately 7.9% of the U.S. population has been diagnosed with asthma, which accounts for 9.6 million office visits per year. Prevalence is increased among patients older than 65 years, women, Black persons, and persons living below the poverty level. Mortality in asthma is significant, with 9.9 deaths per million Americans caused by asthma in 2017; significantly higher mortality is seen among patients who are Black and patients who are older than 65 years.

The onset of asthma can occur at any age, and the natural history varies with the duration and severity of symptoms, sex, and response to therapy. Children often have a family history of atopy or exposure to sensitizing allergens such as dust mites or cockroaches. Childhood asthma may improve or resolve during the teenage and adult years, particularly in males. Adults with new-onset asthma may have occupational exposures known to induce bronchial hyperreactivity. Those with severe symptoms generally have a more sustained course, lower pulmonary function, and increased risk of developing persistent airway obstruction. Diagnosis and treatment of asthma in older adults is often challenged by symptom overlap with other conditions

TABLE 3. Bronchoscopic Diagnostic Procedures

Technique	Description	Examples of Indications
Airway inspection	Visualization of the tracheobronchial tree to the level of segmental airways	Hemoptysis Localized wheeze Persistent atelectasis Diagnosis of tracheobronchomalacia Inhalational injury
Bronchial washings	Samples from large airways	Diagnosis of infections
Bronchoalveolar lavage	Samples from small bronchi and alveoli	Diagnosis of infections Cell counts in diagnosis of parenchymal lung disease Alveolar hemorrhage Cytology for malignancy
Bronchial brushings	Brushings of the endobronchial mucosa for cells	Endobronchial lesions
Endobronchial biopsy	Biopsy within the airway lumen	Endobronchial mass or lesion
Transbronchial lung biopsy	Biopsy of the lung parenchyma or lung nodules/masses using small forceps; often aided by guidance technology, including fluoroscopy, electromagnetic navigation, and radial ultrasonography	Diffuse lung disease Persistent infiltrates Lung nodules/masses Posttransplant rejection
Transbronchial needle aspiration	Aspiration of a lymph node or mass adjacent to the airway	Lymphadenopathy Pulmonary mass Mediastinal mass
Endobronchial ultrasonography	Use of an ultrasound probe at the distal end of the bronchoscope to guide transbronchial needle aspiration	Lymphadenopathy Pulmonary mass Mediastinal mass
Electromagnetic navigation	Images from a recent CT are "linked" with the bronchoscope; an electromagnetic guidance system at the bronchoscope creates a map of the airways and guides the physician to the area of interest	Pulmonary mass or nodule

TABLE 4. Bronchoscopic Therapeutic Procedures

Technique	Description	Examples of Indications
Flexible bronchoscopy	Large airway suctioning Basket and forceps extractions Balloon tamponade of airway	Lobar atelectasis from mucus plugs Foreign body Bleeding
Bronchial thermoplasty	Radiofrequency energy ablation of proximal airway smooth muscle	Severe asthma
Endobronchial stent placement	Bronchoscopic placement of silicon and metal prostheses to expand and support the airways	Malignant obstruction Benign strictures Tracheomalacia or bronchomalacia Anastomotic dehiscence
Airway ablative therapies	Laser therapy Electrocautery Argon plasma coagulation Cryotherapy Brachytherapy	Malignant airway obstruction Benign airway obstruction Airway tumor
Endobronchial valve placement	Airway placement of one-way valves	Bronchopleural fistula Emphysema
Balloon dilation	Targeted endobronchial balloon inflation	Benign or malignant airway stricture

(COPD, heart failure) and the normal effects of aging on pulmonary physiology.

KEY POINT

- Approximately 7.9% of the U.S. population has been diagnosed with asthma, and prevalence is increased among patients older than 65 years, women, Black persons, and persons living below the poverty level.

Pathogenesis

The pathophysiologic mechanisms of asthma include chronic airway inflammation, airway narrowing due to edema, subepithelial fibrosis, smooth muscle hypertrophy, and mucus hypersecretion, in addition to airway smooth muscle constriction causing bronchial hyperreactivity in response to various stimuli. The airway cellular inflammatory profile is variable, persists even during the absence of symptoms, and includes eosinophils, T lymphocytes, mast cells, and neutrophils. Type 2 inflammation with eosinophilia is commonly recognized in allergic asthma, but other cellular profiles exist, with neutrophilic inflammation increasingly recognized in older patients. Bronchial hyperreactivity causing airway obstruction is typically episodic and triggered by stimuli that would not induce symptoms in healthy people. Common triggers include allergens, dusts, fumes, exercise, extremes of temperature, and viral respiratory infections.

Risk Factors

Risk factors for asthma include both host and environmental factors. Genes predisposing to atopy, bronchial hyperreactivity, and airway inflammation have been identified, but genetic predisposition is thought to interact with additional factors, including exposure to indoor allergens (mites, furred animals, cockroaches, molds), outdoor allergens (pollens, molds), tobacco smoke, occupational sensitizers and allergens, viral respiratory infections, and air pollution. In addition, obesity is an important risk factor for asthma.

Asthma is heterogeneous, but distinct phenotypes are recognized and have implications for underlying mechanisms, treatment, and outcomes. Although specific phenotypes are not yet broadly accepted, many are commonly described. These subsets tend to have different cellular compositions of airway inflammation and may respond variably to anti-inflammatory therapies.

KEY POINT

- Genetic predisposition to asthma is thought to interact with additional factors, including exposure to indoor allergens (mites, furred animals, cockroaches, molds), outdoor allergens (pollens, molds), tobacco smoke, occupational sensitizers and allergens, viral respiratory infections, and air pollution.

Symptoms and Clinical Evaluation

Common symptoms of asthma are cough, wheezing, chest tightness, and shortness of breath. They occur intermittently and in response to various stimuli, including allergens, infections, dusts, fumes, and exercise. Symptoms often have a diurnal variation, worsening in the evening and early morning. Viral respiratory infections are a particularly robust trigger for most patients. Variability of symptoms (both improvement and worsening of symptoms over time) is a key diagnostic feature of asthma.

History taking should establish whether the patient has ever smoked tobacco or other products, has pets, or has had environmental exposures to dust, fumes, or particulate matter known to cause bronchial hyperreactivity. A personal or family history of atopy or allergic sinus disease may be present. In particular, the presence of nasal polyps, sensitivity to aspirin, and wheezing is known as the "asthmatic triad." The physical examination may demonstrate wheezing, reduced airflow, or a prolonged expiratory phase. However, patients may also have a completely normal respiratory exam, particularly when they are symptom-free.

Confirmation of reversible airflow obstruction is a cornerstone of asthma diagnosis and can be assessed by spirometry—with measurement of FEV_1, FVC, and the FEV_1/FVC ratio—or by serial measurement of peak expiratory flow rates. Airway obstruction that improves with bronchodilators, improves on subsequent measurements, or improves after 4 weeks of anti-inflammatory treatment supports a diagnosis of asthma. For adults, a significant change in FEV_1 is an increase from baseline of at least 12% and at least 200 mL. For some patients, airflow obstruction is not present during the initial evaluation, and demonstration of bronchial hyperreactivity with bronchial challenge testing is indicated. This is usually performed with inhaled methacholine, although other stimuli (exercise, mannitol) have been validated. If a bronchial challenge test is negative, it is unlikely that a patient has asthma. A positive challenge test confirms bronchial hyperreactivity but is not sufficient to confirm asthma because other disorders may also demonstrate this finding. Therefore, clinical correlation of this finding with symptoms and other testing is needed. Fractional exhaled nitric oxide testing is conditionally recommended as an adjunct in asthma evaluation for those aged 5 years and older. Specific recommendations for use of nitric oxide testing are when the diagnosis of asthma is uncertain after standard evaluation or when spirometry cannot be performed (conditional recommendation), as well as in persistent allergic asthma and uncertainty in choosing, monitoring, or adjusting medications (conditional recommendation).

A chest radiograph is helpful in many patients to rule out other diagnoses, such as COPD, heart failure, parenchymal lung disorders, central airway obstruction, and bronchiectasis. This is especially important in older adults, in whom asthma is often underrecognized and undertreated.

KEY POINTS

- Common symptoms of asthma are cough, wheezing, chest tightness, and shortness of breath; they are intermittent and occur in response to various stimuli, including allergens, infections, dusts, fumes, and exercise.
- Confirmation of reversible airflow obstruction with bronchodilators is a cornerstone of asthma diagnosis and can be made by spirometry, with measurement of FEV_1 or FVC showing an increase from baseline of ≥12% and ≥200 mL.
- In patients with clinical symptoms suggestive of asthma but with normal spirometry, bronchial challenge testing (such as with methacholine) may be helpful to evaluate for asthma; a negative test excludes asthma, whereas a positive test requires clinical correlation.

Asthma Syndromes

Allergic Asthma

Identifying the presence of atopy can determine an allergic asthma phenotype in a patient with respiratory symptoms. The key constituents of the atopic response (activated eosinophils and IgE) are generated by pathways involving cytokines secreted mainly by Th2 cells, and this class of asthmatic airway inflammation is referred to as type 2. It is estimated that at least half of all patients with asthma have type 2 airway inflammation. Biomarker evaluation in these patients often demonstrates serum or sputum eosinophilia or high IgE levels with elevated FeNO. Other common tests to identify atopy include allergy skin-prick tests, which may be administered in the outpatient setting by qualified personnel, and laboratory measurement of allergen-specific IgE in serum. Results of each method are generally concordant. Skin testing is more sensitive but subject to errors related to administration, whereas serum tests are more specific but have higher costs. A normal level of total serum IgE does not preclude clinical allergies. In patients with severe disease, elevated levels of IgE and eosinophils are therapeutic targets for biologic therapies.

Cough-Variant Asthma

Patients with asthma whose primary symptom manifestation is chronic cough without other symptoms are considered to have cough-variant asthma. Diagnosis requires documentation of bronchial hyperreactivity, as most patients will have normal baseline spirometry. Recommended therapies are the same as those for other types of asthma. Other causes of chronic cough, including gastroesophageal reflux and upper airway cough syndrome due to rhinitis, should be investigated. Frequently, these etiologies coexist and require concomitant therapy (see MKSAP 19 General Internal Medicine 1).

Exercise-Induced Bronchoconstriction

Exercise-induced bronchoconstriction (EIB) refers to acute, measurable airway obstruction that occurs in response to exercise. EIB is one of the most common triggers of symptoms in patients with known asthma, and it also occurs in patients without asthma, typically elite athletes, during periods of high-intensity exercise. Environmental factors play a key role in precipitating symptoms. Exercise in cold, dry air, such as during winter or in indoor ice rinks; exposure to high levels of trichloramines in swimming pools; and inhalation of airborne particulates and ozone have all been implicated.

Other disorders, such vocal cord dysfunction and cardiac disorders, can mimic EIB; therefore, establishing the presence of bronchial hyperreactivity is crucial to making an accurate diagnosis. For most patients this entails bronchial challenge testing with inhaled agents or, ideally, exercise. For safety, guidelines from the Global Initiative for Asthma no longer recommend treatment of asthma, including EIB, with a short-acting β_2-agonist (SABA) alone. Recommended therapy is either an inhaled glucocorticoid plus SABA when needed or before exercise or low-dose inhaled glucocorticoid-formoterol as needed or before exercise. Nonpharmacologic measures include preexercise warm-up and warming cold air before inhalation (for example, with a mask or scarf).

KEY POINT

- Initial pharmacologic therapy for exercise-induced bronchoconstriction should consist of administration of an inhaled glucocorticoid plus a short-acting β_2-agonist or low-dose inhaled glucocorticoid-formoterol when needed or before exercise.

Occupational Asthma

A careful occupational history is an essential part of asthma evaluation, as it is estimated that 15% of adult asthma is work-related. Occupational asthma includes both asthma that is directly caused by exposure to sensitizing or irritant substances in the workplace and preexisting asthma that is exacerbated by these same factors. Typical sensitizing agents are high-molecular-weight substances, such as proteins, that induce an IgE-mediated immunologic response. Examples include animal and plant allergens, latex, grains, and diisocyanates. Once sensitized, patients may subsequently react to very low levels of exposure. Those at risk include farmers and animal workers, health care workers, latex glove users, bakers, and manufacturers of polyurethane products. A key clinical indicator is the relationship of symptoms to work exposures; patients often improve during weekends and time away from work. Spirometry before and after workplace exposure is a cost-effective way to confirm a suspected diagnosis of occupational asthma. Alternatively, demonstration of bronchial hyperreactivity through bronchial challenge testing or serial peak flow measurements can be used. Treatment consists of reducing exposure to the offending agent through workplace modifications or removing patients from the workplace entirely, in addition to pharmacologic therapy. The overriding principle of treatment should be prevention, which includes workplace interventions to avoid exposures and monitoring for early identification of disease.

KEY POINT

HVC
- A key clinical indicator of occupational asthma is symptom improvement during weekends and time away from work; spirometry before and after workplace exposures is a cost-effective way to confirm a suspected diagnosis.

Reactive Airways Dysfunction Syndrome

Reactive airways dysfunction syndrome is a well-described subset of irritant-induced occupational asthma. This syndrome occurs in patients without preexisting asthma after a single, high-level exposure to fumes, gases, or vapors; usually the exposure is severe enough to prompt immediate medical evaluation. The diagnosis requires evidence of asthmatic symptoms for at least 3 months after the exposure and is confirmed by airway obstruction or bronchial hyperreactivity.

Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease describes asthma and rhinosinusitis that are precipitated by exposure to aspirin or other NSAIDs that inhibit cyclooxygenase-1. Clinical characteristics include an onset in adulthood, airway and peripheral eosinophilia, inflammatory sinusitis with polyposis, and persistent, often severe asthma. Ingestion of triggering substances can cause life-threatening bronchospasm within minutes to hours, sometimes accompanied by rhinorrhea, conjunctival injection, and flushing. Chronic management, in addition to the usual stepped asthma care, includes discontinuing all aspirin and NSAIDs and use of leukotriene-receptor antagonists that target the increased leukotriene production implicated in the mechanism of this particular asthma. Aspirin desensitization can improve control in a significant percentage of patients but requires specialized expertise.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis is an ongoing immunologic response to inhaled *Aspergillus* species that leads to persistent eosinophilic airway inflammation, increased IgE levels (both total and *Aspergillus* specific), and eventually tissue damage with airway remodeling. Patients present with difficult-to-control asthma, productive cough, and expectoration of mucus plugs. Radiographs may demonstrate pulmonary infiltrates and bronchiectasis. The diagnostic criteria are debated but include the presence of asthma, elevated IgE levels, positive skin tests to *Aspergillus* antigens, increased *Aspergillus*-specific IgE and IgG levels, and either central bronchiectasis or infiltrates. Management is aimed at suppressing the enhanced immunologic response with systemic glucocorticoids and reducing the fungal antigenic burden with antifungal agents.

Management of Chronic Asthma

The goals of longitudinal asthma management are to control chronic asthma symptoms, prevent exacerbations, and minimize risks of developing persistent airway obstruction. This should be accomplished by assessing asthma severity, controlling symptoms on an ongoing basis, and then modifying therapies appropriately, using a stepwise approach (**Figure 3**). There are three essential components to the management of asthma:

1. Assessment of symptom control and risk. Standardized, validated questionnaires that can discriminate between well-controlled and inadequately controlled asthma on the basis of patient symptoms include the Asthma Control Test and the Asthma Control Questionnaire. Patients with daytime symptoms less than twice weekly and nocturnal symptoms less than twice monthly during the preceding 4 weeks are considered well controlled. Risk is based on measured lung function and the potential for future exacerbations, which is related to the presence of comorbidities (**Table 5**) and historical features known to predict future exacerbations. Comorbidities such as gastroesophageal reflux disease, sinus disease, obstructive sleep apnea, vocal cord dysfunction, and obesity are common and should be considered and actively managed to reduce symptoms and potentially improve asthma control.
2. Treatment. Once symptoms and risk are established, therapy should be initiated. All patients with asthma should be provided with rescue medication to use as needed for symptoms. Controller medications are used as maintenance therapy to control symptoms and prevent exacerbations. A critical component of this therapy is teaching and assessing proper inhaler technique; patients require skill and training to effectively use these devices. Use of a spacer can be helpful with compatible inhaler devices.
3. Review response and adjust therapy. Patients should be reassessed several months after initiation of asthma therapies for their level of control and tolerance of medications. Controller medications can be stepped up or down with the goal of maintaining symptom control and minimizing medication exposure.

KEY POINTS

- Aspirin-exacerbated respiratory disease describes asthma and rhinosinusitis that are precipitated by exposure to aspirin or other NSAIDs that inhibit cyclooxygenase-1.
- Control of asthma should be assessed with the use of validated questionnaires.
- Inhaler skills training and adherence are essential for successful treatment.

Quick-Relief Medication

All patients with asthma should be provided with quick-relief, or rescue, therapy. SABAs are the preferred medications to quickly reverse bronchospasm and relieve acute asthma

	Intermittent asthma	**Persistent asthma in persons ≥12 years of age**				
Treatment	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
Preferred	SABA as needed[a] OR ICS and SABA[b] as needed	Daily low-dose ICS and SABA as needed OR Concomitant ICS and SABA as needed	Daily and as-needed combination low-dose ICS-formoterol	Daily and as-needed combination medium-dose ICS-formoterol	Daily medium- to high-dose ICS-LABA + LAMA and SABA as needed	Daily high-dose ICS-LABA + oral glucocorticoid + SABA as needed Consider add-on anti-IgE, anti-IL-5, anti-IL-5R, anti-IL-4/IL-13
Alternative		Daily LTRA + SABA as needed	Daily medium-dose ICS + SABA as needed OR Daily low-dose ICS-LABA or ICS-LAMA, and SABA as needed	Daily medium-dose ICS-LABA or ICS-LAMA, and SABA as needed	Daily medium- to high-dose ICS-LABA and SABA as needed Consider add-on anti-IgE, anti-IL-5, anti-IL-5R, anti-IL-4/IL-13	

← **Assess control** →

Use of objective measures, self-report, and health care utilization

Step up if needed (first check adherence, inhaler technique, environmental factors, and comorbidities)

Step down if possible (and asthma is well controlled x 3 months)

- At each step, include patient education, environmental control, and management of comorbidities.
- For steps 2-4: Consider subcutaneous allergen immunotherapy for patients whose asthma is controlled at initiation, buildup, and maintenance phases.
- If step 4 care or higher is needed, consult with an asthma specialist.

Quick relief for all patients:

- SABA as needed for symptoms: up to 3 treatments at 20-minute intervals as needed
- In steps 3 and 4, ICS-formoterol 1-2 puffs as needed up to a maximum total daily dosage of 12 puffs (54 μg)
- Use of SABA >2 days a week (not prevention of EIB) indicates inadequate control and the need to step up therapy

FIGURE 3. Stepwise approach to asthma therapy. 2020 guidelines from the National Asthma Education and Prevention Program (NAEPP) recommend that all adults and adolescents with mild persistent asthma use a daily inhaled glucocorticoid with an as-needed SABA or use both on an as-needed basis. Those with moderate persistent asthma should use a single inhaler with glucocorticoids and formoterol daily plus additional doses of the combination regimen as needed (known as single maintenance and reliever therapy, or SMART). For step-up therapy, daily medium- to high-dose inhaled glucocorticoids and long-acting β_2-agonist (LABA) plus long-acting muscarinic antagonist (LAMA) and SABA as needed should be used. EIB = exercise-induced bronchospasm; ICS = inhaled corticosteroid (glucocorticoid); IL = interleukin; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; SABA = short-acting β_2-agonist.

[a] National Asthma Education and Prevention Program (NAEPP) recommendation.

[b] Global Initiative for Asthma recommendation.

National Heart, Lung, and Blood Institute. *2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group.* National Institutes of Health; December 2020:28. NIH publication 20-HL-8140. Accessed June 22, 2021. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

TABLE 5. Common Asthma Comorbidities

Comorbidity	Symptoms	Diagnosis and Treatment
Gastroesophageal reflux disease (GERD)[a,b]	Frequently coexists in patients with asthma May be an independent cause of respiratory symptoms such as cough and chest pain	Empiric trial of a proton pump inhibitor for 2 months Consider further testing such as endoscopy and 24-hour esophageal pH monitoring if symptoms do not improve
Sinus disease	Allergic rhinitis: rhinorrhea, nasal obstruction, itching, and sneezing; symptoms can be seasonal, intermittent, or perennial (usually caused by persistent exposure to indoor allergens such as dust mites) Chronic rhinosinusitis: additional symptoms of facial pain, sinus pressure, and sometimes anosmia	Intranasal glucocorticoids For severe cases, consider adding: Intranasal H_1-antihistamines Oral antileukotrienes Oral glucocorticoids Immunotherapy Biologic targeting IgE or eosinophils
Obstructive sleep apnea[b]	Snoring, excessive daytime sleepiness, and witnessed apneas More common in patients with asthma than those without asthma Worsens asthma control, increases asthma-related health care use, and reduces quality of life	Confirm with polysomnography or home sleep testing Positive airway pressure: improves asthma symptoms, quality of life, bronchodilator use, and peak flow rates
Vocal cord dysfunction (VCD)	Inspiratory breathlessness, with throat tightness or voice dysfunction during attacks Caused by paradoxical adduction of the vocal cords during inspiration, causing functional upper airway obstruction Often triggered by exercise, exposure to fumes or irritants, and stress May mimic or coexist with asthma	Laryngoscopy demonstrating paradoxical vocal cord adduction during a symptomatic episode Patients often asymptomatic when evaluated or unable to tolerate laryngoscopy during an acute episode Trial of treatment with speech therapy Also address factors known to worsen VCD (GERD, postnasal drip)
Obesity[c]	Symptoms Dyspnea, wheezing Higher prevalence of asthma with poorer symptom control compared with patients with asthma and normal BMI; and not as responsive to standard controller therapies May confound asthma diagnosis because of overlapping symptoms of breathlessness and exertional wheezing	BMI measurement and objective documentation of reversible airway obstruction in all patients undergoing asthma evaluation Weight loss: improves asthma control and lung function Bariatric surgery: greater amounts of weight loss correlate with better outcomes

[a] See MKSAP 19 Gastroenterology and Hepatology: Disorders of the Esophagus section.

[b] See Sleep Medicine section.

[c] See MKSAP 19 General Internal Medicine 2: Obesity section.

symptoms; however, new safety information suggests that they should only be used in combination with inhaled glucocorticoids (**Table 6**). SABAs have a rapid onset of action and deliver medications directly through the airways, reducing systemic adverse effects. Their main mechanism of action is induction of airway smooth muscle relaxation using stimulation of β_2-agonist receptors. SABAs are generally not administered on a scheduled basis nor as the sole agent. Albuterol is the most commonly used SABA in the United States. While the National Asthma Education and Prevention Program continues to recommend as-needed SABA for intermittent asthma, the Global Initiative for Asthma now recommends that all adults and adolescents with asthma should receive one of three inhaled glucocorticoid combination regimens to reduce the risk for serious exacerbations and to control symptoms:

1. For mild asthma, an inhaled glucocorticoid-formoterol combination as needed or a low-dose inhaled glucocorticoid whenever a SABA is taken (note that both combinations are off-label use)
2. A regular inhaled glucocorticoid or inhaled glucocorticoid plus an inhaled long-acting β_2-agonist (LABA) daily, plus an as-needed SABA
3. Maintenance and rescue treatment with inhaled low-dose budesonide plus formoterol

TABLE 6. Asthma Medications

Drug	Formulations	Adverse Effects
Short-Acting β_2-Agonists		
Albuterol	HFA-MDI, nebulizer solution	Tachycardia and hypokalemia Should not be used as monotherapy
Levalbuterol	HFA-MDI, nebulizer solution	
Short-Acting Anticholinergics (Muscarinic Antagonists)		
Ipratropium bromide	HFA-MDI, nebulizer solution	Dry mouth, tachycardia, acute narrow-angle glaucoma (rare)
Albuterol/ipratropium bromide	HFA-MDI, nebulizer solution	Same and combined effects of both drug classes
Long-Acting β_2-Agonists		
Formoterol[a]	DPI	Tremor, tachycardia; black box warning for use of long-acting β_2-agonist monotherapy in asthma
Salmeterol	DPI	
Arformoterol[a]	Nebulizer solution	
Formoterol fumarate[a]	Nebulizer solution	
Olodaterol[a]	SMI	
Indacaterol maleate[a]	DPI	
Long-Acting Muscarinic Antagonists (Anticholinergics)		
Tiotropium	DPI, SMI	Dry mouth, tachycardia, urinary retention, acute narrow-angle glaucoma (rare)
Aclidinium bromide	DPI	
Umeclidinium	DPI	
Glycopyrrolate	DPI	
Inhaled Glucocorticoids		
Beclomethasone	HFA-MDI	Dysphonia, xerostomia, oral candidiasis, bruising, pneumonia; low incidence of oral glucocorticoid adverse effects
Budesonide	DPI, nebulizer solution	
Fluticasone propionate	HFA, DPI	
Fluticasone furoate	DPI	
Mometasone	DPI	
Ciclesonide	HFA-MDI	
Flunisolide	HFA-MDI	
Inhaled Glucocorticoids and Long-Acting β_2-Agonists		
Budesonide and formoterol[a]	HFA	Same as combined effects of both drug classes
Fluticasone and salmeterol	HFA, DPI	
Mometasone furoate and formoterol fumarate[a]	HFA	
Fluticasone furoate and vilanterol[a]	DPI	
Oral Glucocorticoids		
Prednisone	Tablet, liquid	Bruising, adrenal suppression, osteoporosis, glaucoma, diabetes mellitus, opportunistic infection, insomnia, cataracts, hypertension, weight gain, myopathy, acne
Prednisolone	Tablet, liquid	
Methylprednisolone	IV infusion, tablet	
Leukotriene-Modifying Agents		
Montelukast	Tablet	Headache; rarely liver disease; neuropsychiatric events, including suicidal thoughts and actions
Zafirlukast	Tablet	
Zileuton (5-lipoxygenase inhibitor)	Tablet	
Biologic Agents		
Omalizumab (anti-IgE)	Subcutaneous injection	Anaphylaxis, increased risk for malignancy
Mepolizumab (anti-IL-5)	Subcutaneous injection	
Reslizumab (anti-IL-5)	IV infusion	
Benralizumab (anti-IL-5)	Subcutaneous injection	
Dupilumab (anti-IL-4 and IL-13)	Subcutaneous injection	
Other		
Theophylline	Tablet, capsule, liquid	Tachycardia, nausea, overdose can be fatal

DPI = dry powder inhaler; HFA = hydrofluoroalkane; IL = interleukin; IV = intravenous; MDI = metered dose inhaler; SMI = soft mist inhaler.

[a] Relief of acute bronchospasm is an off-label indication for this medication.

Short-acting inhaled anticholinergics are less effective than SABAs at relieving acute bronchospasm; however, they may be used as adjunctive therapy to SABA treatment in the management of acute exacerbations in the emergency department. This combination has been shown to reduce hospital admission rates.

KEY POINTS

- All patients with asthma should be provided with quick-relief, or rescue, therapy.
- The most recent Global Initiative for Asthma guidelines recommend one of three inhaled glucocorticoid combination regimens: an inhaled glucocorticoid-formoterol combination as needed or low-dose inhaled glucocorticoid whenever a short-acting β_2-agonist (SABA) is taken; a daily inhaled glucocorticoid or inhaled glucocorticoid plus inhaled long-acting β_2-agonist, plus an as-needed SABA; or maintenance and rescue treatment with low-dose budesonide-formoterol.

Controller Medications

Controller medications are used to provide ongoing symptom relief and to prevent asthma exacerbations. Several different classes of controllers exist that target different mechanisms of the asthmatic profile; therefore, medications can be effectively combined to achieve good control. The choice of therapy generally depends on the assessment of risk and is adjusted on the basis of symptom response and patient tolerance (see Figure 3 and Table 6).

Inhaled glucocorticoids are the most effective class of asthma controller medications. These agents alleviate several pathologic processes that make up the asthmatic response, including airway mucosal edema, mucus hypersecretion, and airway inflammation. Adverse effects are dose-related and vary with the steroid formulation. They relate to local deposition (oral candidiasis, dysphonia) and can sometimes be generalized as a result of some degree of systemic absorption. Systemic adverse effects such as adrenocortical suppression, reduced bone mineral density, and cataracts do not generally occur at doses below 400 µg of inhaled budesonide daily or equivalent doses of other inhaled glucocorticoid formulations. An increased rate of pneumonia is found with high-dose and high-potency formulations. Despite these risks, use of inhaled glucocorticoids to prevent the need for oral glucocorticoids should outweigh the potential adverse effects. In active smokers, the effectiveness of these medications is diminished and higher dosing may be required.

Inhaled LABAs that provide sustained airway dilation with just once- or twice-daily dosing are an important tool for asthma treatment. When added to an inhaled glucocorticoid, they provide improved control and decrease the risk for exacerbation. For patients whose asthma is not adequately controlled by a low- or medium-strength inhaled glucocorticoid and SABA as needed, the recommended next step is the addition of formoterol (a LABA) as combined therapy with an inhaled low-dose glucocorticoid in a single inhaler device. Administration in a single inhaler is preferred because of greater adherence and reduced cost compared with administration of each drug in a separate inhaler. Single-agent use of LABAs is not recommended because of the demonstrated increased risk for asthma-related death when used without a simultaneous controller medication. However, five large clinical trials showed that LABAs, when used with inhaled glucocorticoids, did not significantly increase the risk for asthma-related hospitalization, intubation, or death compared with inhaled glucocorticoids alone, and resulted in significantly fewer asthma exacerbations.

Leukotriene-receptor antagonists have a modest bronchodilation effect and treat upper airway conditions such as allergic rhinitis. Patients with aspirin-exacerbated respiratory disease often respond well to these agents.

Oral glucocorticoids are a cornerstone of therapy for the treatment of acute asthma exacerbations, but long-term use exposes patients to the well-known adverse effects of these agents (see Table 6).

Long-acting muscarinic antagonists (LAMAs) provide sustained airway dilation, and tiotropium has been shown to improve lung function and reduce exacerbations when added to therapy in patients not controlled with inhaled glucocorticoid–LABA combination therapy. For patients with excessive adverse effects from LABAs, a LAMA can reasonably be substituted. However, there is not substantial evidence that LAMAs, instead of LABAs, should be the first choice for long-acting airway dilation.

Newer antibody therapies directed against specific mediators of the asthmatic response can be used in patients with severe asthma not adequately controlled on standard therapy, and they have significantly altered the treatment paradigm for these patients. Several types of biologic therapies are now available, and more are in development. The currently available agents are directed against type 2 inflammation and target pathways involved in the activation of eosinophils and IgE production. It is estimated that at least half of patients with asthma have type 2 airway inflammation. In a process referred to as phenotyping, clinically recognizable characteristics are combined with biomarkers to determine whether patients have type 2 inflammation that could benefit from specific biologic treatments. Clinical characteristics suggesting a type 2 high phenotype include atopy, seasonal exacerbations, hay fever, and allergen sensitization. If patients have atopy, as documented by skin testing or elevated serum allergen-specific IgE with high total IgE levels, they can benefit from the anti-IgE biologic omalizumab. Omalizumab is a monoclonal antibody that binds IgE and has been shown to reduce exacerbations in patients with severe persistent asthma despite therapy with high-dose inhaled glucocorticoid and LABA therapy and, often, additional pharmacologic therapies. Patients with eosinophilia can be treated with inhibitors of interleukins involved in eosinophilic recruitment and maturation. These include mepolizumab, reslizumab, and benralizumab, which target interleukin-5 (IL-5), or dupilumab, an inhibitor of IL-4 and IL-13. The level of blood eosinophilia that predicts efficacy varies for each agent and ranges from an absolute eosinophil count of 150 cells/µL (0.15 × 109/L) to 400 cells/µL (0.4 × 109/L), regardless of IgE level.

Both anti-IgE and anti-interleukin therapies reduce symptoms, need for oral glucocorticoids, and exacerbations in eligible patients with moderate or severe persistent asthma. These treatments are expensive and should only be considered after verifying patient adherence with asthma medications, assessing inhaler technique, and addressing any comorbid conditions. Nonetheless, omalizumab reduces emergency department visits and may be cost-effective in eligible patients with moderate to severe atopic asthma that is not well controlled with other therapies.

KEY POINTS

- Inhaled glucocorticoids are the most effective class of asthma controller medications.
- For patients whose asthma is not adequately controlled by a moderate-strength inhaled glucocorticoid, the addition of a long-acting β_2-agonist as combined therapy with an inhaled low-dose glucocorticoid in a single inhaler device is the recommended next step.
- Single-agent use of long-acting β_2-agonists is not recommended because of the demonstrated increased risk for asthma-related death when used without another controller medication.
- Targeting elevated IgE or eosinophil levels with antibody therapies in eligible patients with severe persistent allergic asthma despite standard therapy reduces symptoms, need for oral glucocorticoids, and exacerbations.

Nonpharmacologic Therapy

Comprehensive asthma care strategies include avoidance of triggers with allergen management (mold abatement, pest control, air filters), reduced exposure to environmental tobacco smoke, and a healthy diet and exercise program to promote weight loss.

Bronchial thermoplasty is a radiofrequency airway treatment administered using bronchoscopy that can reduce exacerbations and improve quality of life. Candidates are patients with an FEV_1 higher than 60% and severe asthma that is poorly controlled despite high-dose inhaled glucocorticoid–LABA combination therapy.

Management of Asthma Exacerbations

Asthma exacerbation refers to an acute worsening of symptoms or lung function from baseline that necessitates a step up in therapy (see Figure 3). Prompt recognition and treatment of asthma exacerbations are needed to relieve symptoms and prevent hospitalizations. All patients with asthma should have a written asthma management plan that helps them recognize the symptoms of an exacerbation and begin self-treatment. Clinicians should screen for patient factors that contribute to an increased risk for death from asthma and counsel patients appropriately (**Table 7**). Self-treatment of an exacerbation consists of frequent use of reliever medications; increasing the dose, frequency, or both of controller medications; and adding a short course of oral glucocorticoids (typically 5-7 days of prednisone 40-50 mg/d). Patients who do not improve with self-care or who have signs that indicate a severe attack should be evaluated in an acute care facility. Management there should include close monitoring of dyspnea, work of breathing, and vital signs; treatment should include frequent inhaled SABA administration, prompt glucocorticoid therapy, and administration of supplemental oxygen to maintain oxygen saturation above 93%. For further discussion of severe asthma exacerbations, see Common ICU Conditions.

TABLE 7. Severe Asthma Exacerbation Risk Factors and Signs

Risk Factors for Asthma-Related Death
History of near-fatal asthma attack or intubation
Emergency department or hospital visit in the last 12 months
Poor asthma medication adherence or not using inhaled glucocorticoid
Current or recent treatment with oral glucocorticoid
Psychosocial stressors or psychiatric disease
Food allergy
Overuse of short-acting β_2-agonist
Signs of a Severe Asthma Exacerbation
Unable to speak in full sentences
Use of accessory muscles of respiration
Respiration rate >30/min, heart rate >120/min
SpO_2 <90% on ambient air
Agitation, confusion, or drowsiness

SpO_2 = oxygen saturation as measured by pulse oximetry.

KEY POINT

- All patients with asthma should have a written asthma management plan that helps them recognize the symptoms of an exacerbation and begin self-treatment.

Severe Refractory Asthma

Severe refractory asthma is present in patients who require high doses of an inhaled glucocorticoid plus a second controller or oral glucocorticoids to prevent worsening, or who experience two or more exacerbations within 1 year that require an emergency department visit or hospitalization. This group of patients consumes the most asthma-related health care resources. It is important to verify the diagnosis in these patients and to document medication compliance and correct inhaler technique before considering additional therapies. In addition, comorbidities should be aggressively managed. Treatment guided by specific phenotypes can be helpful in this group, such as biologic agents for patients with high IgE or eosinophil levels and leukotriene-receptor antagonists for patients with aspirin sensitivity. Referral to a team of subspecialists is often indicated.

Asthma in Pregnancy

Pregnant patients should be advised that the advantages of asthma treatment are significantly greater than the potential risk to the fetus from asthma therapies. Pregnancy can affect asthma control, leading to either worsening or improvement, and patients should be closely monitored for signs of exacerbation, which occurs most frequently during the second trimester. Inhaled glucocorticoids, oral glucocorticoids, SABAs, leukotriene-receptor antagonists (montelukast, zafirlukast), and LABAs have all been used extensively during pregnancy without data to suggest fetal harm.

Chronic Obstructive Pulmonary Disease

Definition

COPD is a chronic lung disease defined by persistent respiratory symptoms and airflow limitation or obstruction that is not fully reversible.

Epidemiology

COPD is a common disorder that currently affects more than 6% of the U.S. population. The worldwide prevalence continues to rise, and the World Health Organization predicts that by 2030 COPD will become the world's fifth most prevalent disorder and the third leading cause of death. COPD is associated with high morbidity and mortality and is the fourth leading cause of death in the United States.

Pathophysiology

COPD is an inflammatory condition. Cigarette smoke and other irritants activate both macrophages and epithelial cells within the respiratory tract. The epithelial cells then release several neutrophil chemotactic factors. Macrophages and neutrophils release proteases that cause destruction of lung parenchyma. Proteases are typically inactivated by antiproteases, such as α_1-antitrypsin, which may also be reduced in COPD. Oxidative stress from irritants and inflammatory cells may lead to additional inflammation and tissue destruction. Ultimately, patients develop fibrosis of the small airways and reduced elastic recoil of the lungs leading to static hyperinflation; in addition, mucin concentrations are abnormally elevated. As the degree of inflammation increases, airflow obstruction worsens and the ability to fully exhale decreases. Inhalation is initiated before exhalation is completed, resulting in dynamic hyperinflation—termed air trapping—which is seen as an increased anteroposterior diameter of the chest and flattening of the diaphragm on chest radiographs. The diaphragmatic flattening limits the ability to increase breath volume during exertion. Compensatory use of accessory muscles to increase tidal volume and increased respiration rate augment minute ventilation. These changes increase the work of breathing and contribute to the sensation of dyspnea in patients with COPD.

Risk Factors

Exposure to cigarette smoke (both first- and secondhand exposure) is the most important risk factor for COPD. Genetic predisposition seems to explain some of the variation in susceptibility to developing COPD when exposed to cigarette smoke. Long-term exposure to other irritants can also result in COPD. This includes exposure to air pollution (both indoor and outdoor) and occupational chemicals and dusts. An important example of indoor air pollution is the use of biomass fuel for cooking inside the home, which is a common risk factor for COPD in the developing world. A family history of COPD is also considered a risk factor for the disease, as is α_1-antitrypsin deficiency.

KEY POINT

- Exposure to cigarette smoke is the most important risk factor for COPD.

Heterogeneity of COPD

COPD is a heterogeneous condition. Some patients present predominately with a chronic productive cough due to mucus hypersecretion, whereas others present predominately with progressive dyspnea secondary to hyperinflation. The heterogeneity extends beyond clinical symptoms. Phenotypic heterogeneity has been characterized on the basis of clinical, physiologic, molecular, and radiographic variables. For example, eosinophilia has been associated with increased responsiveness to glucocorticoids. There also appears to be a subgroup of patients who are more prone to developing acute exacerbations. Understanding such variables could potentially improve the accurate assessment of prognosis and individualize patient care. Because of the heterogeneity of the disease and its presentation, tools have been developed to aid in determining prognosis and best treatment strategies. Several staging assessments exist. For example, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) system combines the degree of airflow obstruction obtained from spirometry with the number of previous exacerbations as well as symptoms to help determine treatment. The BODE index uses the variables of body mass index (B), airflow obstruction (O), dyspnea (D), and exercise capacity (E) to predict outcomes and response to therapy. Airflow obstruction is determined using the postbronchodilator FEV_1 percentage of predicted value for age, sex, height, and race. The BODE index uses the Modified British Medical Research Council (mMRC) dyspnea scale questionnaire to grade perceived dyspnea ranging from dyspnea only with strenuous exercise to dyspnea even when getting dressed. The exercise capacity is determined by the walking distance on a 6-minute walk test. This index provides better prognostic information than the FEV_1 alone and has been used to approximate 4-year survival and risk for hospitalization for COPD.

Comorbid Conditions

Patients with COPD often suffer from comorbid conditions that further increase morbidity and mortality. Some conditions, such as cardiovascular disease, share common risk factors, but others seem to be independently associated with COPD or a consequence of treatment of COPD. These include muscle loss with associated weakness and weight loss, osteoporosis, and depression.

KEY POINT

- COPD is a heterogeneous condition and patients present with variable symptoms, including cough, sputum production, and dyspnea.

Diagnosis

The possibility of COPD should be considered and spirometry should be performed in patients aged 40 years or older with progressive dyspnea, chronic cough, chronic sputum production, or recurrent lower respiratory tract infections, particularly in the presence of known risk factors for the disease, especially smoking. The role of screening spirometry in asymptomatic individuals with risk factors is controversial. The U.S. Preventive Services Task Force guideline recommends against screening for COPD in asymptomatic adults, whereas the GOLD advocates performing screening spirometry in individuals with risk factors for COPD.

In the appropriate clinical context, the diagnosis of COPD is made using spirometric measurement to document airflow obstruction. COPD is confirmed by a postbronchodilator FEV_1/FVC ratio of less than 0.70. This differs from the finding in patients with asthma, whose airflow obstruction is reversible with bronchodilator therapy. Measuring lung volumes and diffusing capacity is not required to diagnose COPD but may help in determining the severity of disease. Clinicians should rule out other causes of chronic respiratory symptoms, including heart failure, bronchiectasis, obliterative bronchiolitis, tuberculosis, and diffuse panbronchiolitis.

KEY POINTS

- The U.S. Preventive Services Task Force guideline does not recommend spirometric screening for COPD in asymptomatic individuals.
- In the appropriate clinical context, COPD is diagnosed by a postbronchodilator FEV_1/FVC ratio of less than 0.70.

Disease Assessment

After a diagnosis of COPD has been established, the initial assessment focuses on disease severity, which is determined using a combination of symptoms, degree of airflow obstruction on spirometry, history of acute exacerbations, and presence of comorbid conditions. Several validated tools are available to assess patients' symptoms, including the COPD Assessment Test, the Clinical COPD Questionnaire, and the mMRC scale (**Table 8**). The GOLD criteria use the COPD Assessment Test or mMRC scale to determine symptom severity, and the BODE index (**Table 9**) requires the use of the mMRC scale. The Clinical COPD Questionnaire is often used to screen patients for symptoms of COPD. Symptoms are then combined with the results from spirometry (**Table 10**) to determine disease severity (**Table 11**).

TABLE 8. Modified Medical Research Council Dyspnea Scale

Score	Description of Dyspnea	Severity
0	I get breathless only with strenuous exercise.	None
1	I get short of breath when hurrying on level ground or walking up a slight hill.	Mild
2	On level ground, I walk slower than other people my age because of breathlessness, or I have to stop for breath when walking at my own pace.	Moderate
3	I stop for breath after walking approximately 100 yards or after a few minutes on level ground.	Severe
4	I am too breathless to leave the house or breathless when dressing.	Very severe

Based on the 1959 MRC Breathlessness Scale, as modified and published in Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report; 28. Accessed September 27, 2020. https://goldcopd.org/gold-reports/. Used with the permission of the Medical Research Council.

Patients who have had two or more acute exacerbations within the last year, who have an FEV_1 of less than 50% of predicted, or who have ever been hospitalized for an acute exacerbation are at high risk for recurrent acute exacerbations. Clinicians should determine whether the patient suffers from any of the common comorbid conditions associated with COPD that indicate a higher morbidity and mortality and treat appropriately.

Pulse oximetry at rest and at exertion should be used to determine the need for supplemental oxygen. Arterial blood gases should be measured to assess for underlying hypercapnia in patients with a low FEV_1, change in mental status, acute exacerbation, elevated level of serum bicarbonate, or oxygen saturation of less than 92% on pulse oximetry.

An α_1-antitrypsin level should be obtained once in all patients with COPD. A pattern of basilar emphysema, associated liver disease or panniculitis, or a strong family history of emphysema in patients with COPD suggests possible α_1-antitrypsin deficiency, but none of these features is sufficiently sensitive for the condition.

TABLE 9. BODE Index to Estimate Prognosis of COPD

Parameter	Points Assigned
BMI	
>21	0
≤21	1
Obstruction of Airflow: FEV$_1$ (Postbronchodilator Percentage Predicted)	
>65%	0
50%-64%	1
36%-49%	2
<35%	3
Dyspnea: mMRC Score	
0-1	0
2	1
3	2
4	3
Exercise Capacity: 6-Minute Walking Distance	
≥350 m	0
250-349 m	1
150-249 m	2
≤149 m	3

BODE = body mass, airflow obstruction, dyspnea, and exercise; mMRC = Modified British Medical Research Council dyspnea scale. Approximate 4-year survival: 0-2 points: 80%; 3-4 points: 67%; 5-6 points: 57%; 7-10 points: 18%.

From Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1007. [PMID: 14999112]. Copyright © 2004 Massachusetts Medical Society. Reproduced with permission from the Massachusetts Medical Society.

KEY POINTS

- After a diagnosis of COPD has been established, the initial assessment focuses on disease severity, which is determined using a combination of symptoms, degree of airflow obstruction on spirometry, history of acute exacerbations, and presence of comorbid conditions.
- Patients who have had two or more acute exacerbations within the last year, who have an FEV$_1$ of less than 50% of predicted, or who have ever been hospitalized for an acute exacerbation are considered to be at high risk for recurrent acute exacerbations.

TABLE 10. Classification of Airflow Limitation Severity in COPD by Spirometry[a,b]

Category	Severity	Spirometry
GOLD 1	Mild	FEV$_1$ ≥80% predicted
GOLD 2	Moderate	50% ≤ FEV$_1$ < 80% predicted
GOLD 3	Severe	30% ≤ FEV$_1$ < 50% predicted
GOLD 4	Very severe	FEV$_1$ <30% predicted

GOLD = Global Initiative for Chronic Obstructive Lung Disease.

[a] In patients with FEV$_1$/FVC less than 0.7.

[b] Based on postbronchodilator FEV$_1$.

Reproduced with permission, from Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report; 27. Copyright 2020, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Fontana, WI, USA.

Management of COPD

A management plan for COPD should include the identification and reversal of risk factors, especially ongoing exposure to cigarette smoke. The severity of a patient's COPD should guide the choice of therapy (**Table 12**). No currently available treatments can prevent long-term decline in lung function, so patients should be monitored for evidence of disease progression that may guide additional therapy. The goals of therapy are to reduce symptoms and improve exercise tolerance and quality of life, as well as to prevent and treat exacerbations, prevent disease progression, and decrease mortality.

Smoking Cessation

Smoking cessation is essential in the management of COPD, as it can slow the decline of FEV$_1$. Clinicians should encourage patients to quit smoking and be aware that the success rates for smoking cessation increase when counseling is combined with medication therapy. All smokers without contraindications should additionally receive at least one of the seven FDA-approved treatments for smoking cessation. The approved medications include nicotine replacement therapies, varenicline, and bupropion (see MKSAP 19 General Internal Medicine 1).

KEY POINT

- Smoking cessation is essential in the management of COPD, as it can slow the decline of FEV$_1$.

TABLE 11. GOLD Model for Classifying Severity of Disease in COPD[a]

Patient Category	Characteristics	Exacerbations Per Year	CAT Score	mMRC Score
A	Low risk, fewer symptoms	≤1, no hospitalization	<10	0-1
B	Low risk, more symptoms	≤1, no hospitalization	≥10	≥2
C	High risk, fewer symptoms	≥2 or ≥1 with hospital admission	<10	0-1
D	High risk, more symptoms	≥2 or ≥1 with hospital admission	≥10	≥2

CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified Medical Research Council dyspnea scale.

[a] See Table 10 for definitions of spirometric classifications.

Information from Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report. Accessed September 27, 2020. https://goldcopd.org/gold-reports/

TABLE 12. Recommended Pharmacologic Management of COPD by GOLD Classification

Patient Group	Recommended Therapy	Alternative Therapy	Other Considerations
A	Short-acting bronchodilator *or* Long-acting bronchodilator	Evaluate effect of therapy and continue, stop, or try alternative bronchodilator as appropriate	All patients in group A should receive bronchodilator therapy based on its effect on dyspnea; therapy should be continued if symptomatic benefit is documented.
B	Long-acting bronchodilator (LABA or LAMA) *or* Combination therapy with two bronchodilators may be considered for patients with severe dyspnea	If symptoms persist after one long-acting bronchodilator, try combined therapy with LABA and LAMA	Long-acting inhaled bronchodilators are superior to short-acting bronchodilators received as needed. There is no evidence to support use of one class of long-acting bronchodilators over another for initial relief of symptoms for patients in group B. In the individual patient, the choice should depend on the patient's perception of symptom relief. Patients in group B are likely to have comorbidities that affect symptoms and prognosis, and these should be investigated.
C	LAMA; if further exacerbations, LAMA and LABA	LABA and inhaled glucocorticoids	LABA and LAMA is preferred to LABA and inhaled glucocorticoids because inhaled glucocorticoids increase the risk of developing pneumonia in some patients.
D	LAMA or LAMA and LABA[a] *or* Inhaled glucocorticoids and LABA[b]	If exacerbations continue, consider: Roflumilast (patients with an FEV_1 <50% of predicted and chronic bronchitis, particularly if they have experienced at least one hospitalization for an exacerbation in the previous year) *or* Macrolide therapy (the best available evidence exists for the use of azithromycin)	Initial therapy with LABA and inhaled glucocorticoids may be appropriate in some patients, including those with a history or findings suggestive of asthma.

GOLD = Global Initiative for Chronic Obstructive Lung Disease; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic agent.

[a] Consider if highly symptomatic.

[b] Consider if eosinophils >300/µL (0.30×10^9/L).

Information from Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report. Accessed September 27, 2020. https://goldcopd.org/gold-reports/

Pharmacologic Therapy

Pharmacologic therapies in COPD are used to reduce symptoms, improve quality of life, and reduce the frequency and severity of exacerbations (**Table 13**). Bronchodilators are mainstays of therapy for COPD irrespective of the severity of the disease. Any time bronchodilators or other inhalers are prescribed, the clinician should ensure that the patient receives education on proper inhaler technique. Recommended initial management is outlined in Table 12.

Bronchodilators

Inhaled bronchodilators include β_2-agonists and anticholinergics/antimuscarinic agents. Both are available as short-acting and long-acting inhalers and improve symptoms and expiratory airflow. SABAs and muscarinic antagonists result in similar bronchodilation, and either can be used as monotherapy. However, dual treatment results in a greater degree of bronchodilation and expiratory airflow, which may lead to symptom benefit in select patients.

If short-acting bronchodilators are insufficient to control symptoms in patients with more severe disease, a long-acting bronchodilator—either a LABA or a LAMA—can be added. Choosing the appropriate long-acting bronchodilator inhaler requires consideration of patient and physician preference, potential adverse effects, and cost. If symptoms persist on monotherapy, the addition of a second long-acting bronchodilator from the alternate bronchodilator class may result in clinical improvement. Long-acting bronchodilators alone should not be used in patients with a history or diagnosis of asthma unless an inhaled glucocorticoid is also prescribed because of the potential for increased risk for mortality in this patient population when a LABA is used without an inhaled glucocorticoid.

TABLE 13. Drugs Used in the Treatment of COPD

Agent	Adverse Effects	Notes
Bronchodilators		
Inhaled short-acting β_2-agonists (albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol, terbutaline)	Tachycardia and hypokalemia (usually dose dependent), but generally well tolerated by most patients	Generally used as needed for mild disease with few symptoms
Inhaled short-acting anticholinergic agents (ipratropium)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors; rarely acute narrow-angle glaucoma; this drug class has been shown to be safe in a wide range of doses and clinical settings	Generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics
Inhaled long-acting anticholinergic agents (tiotropium, aclidinium, umeclidinium, glycopyrrolate)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors; rarely acute narrow-angle glaucoma	Not to be used with ipratropium; use when short-acting bronchodilators provide insufficient control of symptoms
Inhaled long-acting β_2-agonists (salmeterol, formoterol, arformoterol, indacaterol, olodaterol)	Sympathomimetic symptoms such as tremor and tachycardia; overdose can be fatal	Use as maintenance therapy when short-acting bronchodilators provide insufficient control of symptoms; not intended to be used for treatment of exacerbations of COPD or acute bronchospasm
Methylxanthines (theophylline, aminophylline; sustained and short-acting)	Tachycardia, nausea, vomiting, and disturbed sleep; narrow therapeutic index; overdose can be fatal with seizures and arrhythmias	Used as maintenance therapy; generally used only after long-acting bronchodilator treatment to provide additional symptomatic relief of exacerbations; may also improve respiratory muscle function
Oral β_2-agonists (albuterol, metaproterenol, terbutaline)	Sympathomimetic symptoms such as tremor and tachycardia	Used as maintenance therapy; rarely used because of adverse effects but may be beneficial for patients who cannot use inhalers
Oral Phosophodiesterase-4 Inhibitor		
Roflumilast	Diarrhea, nausea, backache, decreased appetite, dizziness	Used to reduce risk for exacerbations in patients with severe COPD with chronic bronchitis and history of exacerbations; roflumilast should not be used with methylxanthines because of potential toxicity
Anti-Inflammatory Agents		
Inhaled glucocorticoids (fluticasone, budesonide, mometasone, ciclesonide, beclomethasone, flunisolide)	Dysphonia, skin bruising, oral candidiasis; rarely adverse effects of oral glucocorticoids (see below)	Most effective in patients with a history of frequent exacerbations and when used in conjunction with long-acting bronchodilators
Oral glucocorticoids (prednisone, prednisolone)	Skin bruising, adrenal suppression, glaucoma, osteoporosis, diabetes mellitus, systemic hypertension, pneumonia, cataracts, opportunistic infection, insomnia, mood disturbance	Use for significant exacerbations of COPD; avoid, if possible, in stable COPD to limit glucocorticoid toxicity; consider inhaled glucocorticoids to facilitate weaning of systemic glucocorticoids
Combination Agents		
Combined inhaled long-acting β_2-agonist and inhaled glucocorticoid in a single inhaler (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol)	Same/combined effects of both drug classes	
Combined short-acting β_2-agonist plus short-acting anticholinergic in a single inhaler (fenoterol/ipratropium, albuterol/ipratropium)	Same/combined effects of both drug classes	Generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics; this combination therapy may be used for maintenance therapy only if patients have well-controlled disease on this combination treatment and do not require rescue therapy if/when expense is a determining factor
Combined inhaled glucocorticoid and ultra-long-acting β_2-agonist in a single inhaler (fluticasone/vilanterol)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm
Combined long-acting anticholinergic plus ultra-long-acting β_2-agonist in a single inhaler (umeclidinium/vilanterol)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm; avoid using both short- and long-acting anticholinergics
Combined long-acting anticholinergic plus long-acting β_2-agonist in a single inhaler (olodaterol/glycopyrrolate, indacaterol/glycopyrrolate, glycopyrrolate/formoterol, olodaterol/tiotropium)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm; avoid using both short- and long-acting anticholinergics
Combined long-acting anticholinergic plus long-acting β_2-agonist plus inhaled corticosteroid in a single inhaler (fluticasone/umeclidinium/vilanterol)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm; avoid using both short- and long-acting anticholinergics

Inhaled Glucocorticoids

Inhaled glucocorticoids are typically used only in combination with a long-acting bronchodilator for treatment of COPD (see Table 12). Inhaled glucocorticoids are not used alone unless a patient is not able to use long-acting bronchodilators (see Table 13). Inhaled glucocorticoids used alone and in combination with long-acting bronchodilators improve lung function and reduce symptoms and exacerbations in patients with moderate to severe COPD, but they are associated with an increased risk for pneumonia. In patients with severe COPD, triple inhaler therapy with a LABA, a LAMA, and an inhaled glucocorticoid may provide additional symptom benefit and reduced exacerbations.

KEY POINTS

- Bronchodilators are the mainstay of therapy for COPD irrespective of the severity of the COPD.
- Any time bronchodilators or other inhalers are prescribed, the clinician should ensure that the patient receives education on proper inhaler technique.

Oral Glucocorticoids

Oral glucocorticoids are recommended for short-duration treatment of acute exacerbations of COPD (see Acute Exacerbations: Goals and Therapeutic Management section). However, long-term use of oral glucocorticoids should be avoided because of the risk for significant adverse effects, including diabetes and osteoporosis.

Methylxanthines

The methylxanthines (aminophylline and theophylline) are now rarely used to treat COPD. Theophylline has been shown to improve functional capacity and reduce the number of exacerbations. However, it has a narrow window between therapeutic and toxic dosages and is therefore only used for patients with advanced COPD who have refractory symptoms not controlled by standard therapy. Studies of the use of either aminophylline or theophylline during acute exacerbations have shown no benefit.

Roflumilast

Roflumilast is a selective phosphodiesterase-4 inhibitor that is used to reduce the frequency of exacerbations in patients with severe COPD who have primarily symptoms of chronic bronchitis.

α_1-Antitrypsin Augmentation Therapy

Antiproteases, including α_1-antitrypsin, typically inactivate proteases that may lead to permanent lung injury. In patients with α_1-antitrypsin deficiency, replacing this enzyme with augmentation therapy may slow the progression of related emphysema. However, it is costly, has not been shown to decrease exacerbations or the rate of FEV_1 decline, and is not effective for the treatment of patients whose COPD is not caused by α_1-antitrypsin deficiency.

Other Agents

Macrolide antibiotics have inflammatory and antimicrobial effects. Long-term macrolide therapy may reduce the frequency of exacerbations when prescribed for patients with severe COPD and a history of frequent exacerbations. Mucolytics and antitussives are not routinely used in the management of COPD but may provide some symptomatic relief in patients with significant sputum production.

Immunization

Immunizations can prevent infections in patients with COPD. Because infections are the most common trigger of acute exacerbations, routine immunizations are recommended for all patients with COPD. Patients should receive the pneumococcal polysaccharide vaccine (PPSV23) and an annual influenza immunization. Immunocompetent patients aged 65 years and older should be engaged in shared decision making regarding vaccination with the pneumococcal conjugate vaccine (PCV13). (See MKSAP 19 General Internal Medicine 2: Routine Care of the Healthy Patient/Immunization section.)

KEY POINTS

- Oral glucocorticoids are recommended for short-duration treatment of acute exacerbations of COPD; long-term use of oral glucocorticoids should be avoided.
- All patients with COPD should have the pneumococcal polysaccharide vaccine and an annual influenza immunization.

Nonpharmacologic Therapy

Pulmonary Rehabilitation

Pulmonary rehabilitation is a comprehensive program that combines exercise training, nutritional support, education, and social support for patients with chronic lung conditions. It has been shown to relieve symptoms, improve quality of life, and decrease frequency of hospitalizations in patients with COPD. Clinicians should consider adding this to appropriate medical therapy in patients with a GOLD severity group of B, C, or D, and particularly in those recently hospitalized after an exacerbation.

Oxygen Therapy

The use of supplemental oxygen has been shown to improve quality of life and decrease mortality in patients with COPD and resting hypoxemia with an arterial Po_2 of 55 mm Hg or less or an oxygen saturation (as measured by pulse oximetry) of 88% or less. Patients with cor pulmonale, heart failure, or erythrocytosis should be offered the use of supplemental oxygen if their Po_2 is 59 mm Hg or less or their oxygen saturation is 89% or less. Some patients may not qualify for oxygen at rest but may desaturate during sleep, exertion, or air travel. Supplemental oxygen is typically prescribed if the oxygen saturation as measured by pulse oximetry falls below 89% in these situations, but the benefits are less defined.

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NPPV), also termed noninvasive mechanical ventilation, can be used for acute and chronic respiratory failure. For patients with a COPD exacerbation and acute hypercapnic respiratory failure with acidosis, NPPV improves symptoms and reduces intubation rates, lengths of hospital stay, and mortality. It may also be beneficial in patients with COPD who have pneumonia to help with discontinuing mechanical ventilation and for palliative care. It does not replace intubation and mechanical ventilation in critically ill patients, comatose patients, or patients who have sustained a cardiac arrest. NPPV is generally well tolerated, and improvement of the pH and Pco_2 within 1 to 2 hours predicts success. Adding home NPPV to oxygen therapy in patients with persistent hypercapnia after an acute exacerbation of COPD prolongs the time to readmission and death.

Prognosis and Goals of Care

The current GOLD initiative recommends combining the degree of airflow limitation using the postbronchodilator FEV_1 with the number of exacerbations and the patient's symptoms to classify the severity of disease. This will allow the clinician to guide escalation or deescalation of medical therapies as appropriate (see Tables 10, 11, and 12).

The BODE index (see Table 9) can be used as a prognostic indicator for patients with COPD to approximate 4-year survival.

In patients with severe disease with an overall poor prognosis, referral for palliative care or hospice can provide significant improvements in symptom burden. Palliative care can significantly aid in symptom management in patients with COPD at any stage of disease. Patients experience not only dyspnea but also anxiety and depression, which may also be addressed. Opioids are commonly used to treat dyspnea that persists despite medical therapy. Guidelines suggest a patient with severe COPD—defined by disabling symptoms despite medical therapy, progression of disease as evidenced by increasing emergency department evaluations or hospitalizations, and hypoxemia or hypercapnia—should be considered for hospice care.

KEY POINT

- Guidelines suggest that a patient with severe COPD (defined by disabling symptoms despite medical therapy, progression of disease as evidenced by increasing emergency department evaluations or hospitalizations, and hypoxemia or hypercapnia) should be considered for hospice care.

Lung Volume Reduction Therapy

The National Emphysema Treatment Trial demonstrated that patients with upper-lobe-predominant emphysema and significant exercise limitations even after participation in a pulmonary rehabilitation program had improved quality of life, exercise tolerance, pulmonary function, and survival with lung volume reduction surgery. A key finding from the National Emphysema Treatment Trial was that patient selection was critical to success and that patients with an FEV_1 of less than 20% of predicted, a diffusing capacity of less than 20% of predicted, or non-upper-lobe-predominant disease had a high operative mortality and should not be offered lung volume reduction surgery. Nonsurgical lung volume reduction procedures, including bronchoscopic placement of endobronchial valves or plugs and thermal ablation of the airway, are being studied for treatment of emphysematous changes in patients with COPD. Early results suggest that patients with severe air trapping and hyperinflation may get the most benefit from these new techniques. Patient selection criteria for surgical lung volume reduction also apply to nonsurgical techniques.

Lung Transplantation

Referral for lung transplantation can be considered in patients with severe COPD. The decision to refer should depend on the patient's life expectancy, quality of life, and preferences. In general, patients at high risk of dying in less than 2 years who have a high probability of 90-day postoperative survival are candidates. Patients with an elevated BODE index (5 or 6), resting hypoxemia, hypercapnia, an FEV_1 of less than 25% of predicted, or significant exercise limitation despite medical therapy, smoking cessation, and participation in a pulmonary rehabilitation program may be referred for evaluation for lung transplantation. Transplantation improves quality of life, and the median life expectancy is 5.5 years.

Acute Exacerbations

Definition

An acute exacerbation of COPD is a worsening of a patient's typical symptoms that leads to a change in medical therapy or requires hospitalization. Most commonly, exacerbations are manifested by an increase in the severity or frequency of cough, worsening dyspnea, and an increase in the amount or change in the character of sputum produced. Most exacerbations are triggered by a respiratory infection (either viral or bacterial), smoking, and environmental exposures. An exacerbation can be triggered by other causes, and in some cases no trigger is identified. Studies suggest that exacerbations are underreported by patients and result in adverse outcomes.

KEY POINT

- An acute exacerbation of COPD is a change in a patient's typical symptoms that leads to a change in medical therapy or hospitalization; the most common symptoms of exacerbations are an increase in the severity or frequency of cough, worsening dyspnea, and an increase in the amount or change in the character of sputum produced.

Prevention

Acute exacerbations of COPD can have substantial effects on quality of life and health care costs, and they may accelerate the decline in lung function and increase mortality. It is therefore important to prevent exacerbations whenever possible. Strategies to prevent exacerbations include smoking cessation, participating in pulmonary rehabilitation programs when appropriate, receiving recommended immunizations, and ensuring proper inhaler technique and use of medications. Long-term use of azithromycin or roflumilast has also been shown to prevent future exacerbations in patients who have a history of frequent exacerbations.

KEY POINT

- Strategies to prevent COPD exacerbations include smoking cessation, participating in pulmonary rehabilitation programs when appropriate, receiving recommended immunizations, and ensuring proper inhaler technique and use of medications.

Initial Assessment and Setting of Care

The first steps in managing a patient with a presumed COPD exacerbation are to confirm the diagnosis and determine the severity of the exacerbation. A mild exacerbation is one that can be managed solely by short-acting bronchodilators. A moderate exacerbation requires treatment with antibiotics, glucocorticoids, or both. A severe exacerbation is defined by the need for an evaluation in the emergency department or hospitalization. Patients with respiratory distress or who are at risk of developing respiratory distress should be hospitalized; additional testing, including a chest radiograph, electrocardiogram, complete blood count, and basic metabolic panel, should be obtained to rule out other causes or comorbidities contributing to the acute presentation. Oxygen saturation should be measured by pulse oximetry. Arterial blood gas measurement is recommended for patients with a severe exacerbation to determine the presence of hypercapnia or hypoxemia. A sputum culture is not routinely used to assess COPD exacerbations as it rarely affects management. Patients with mild symptoms may not require any additional testing.

KEY POINTS

- Patients who have COPD and respiratory distress or who are at risk of developing respiratory distress should be hospitalized and evaluated with a chest radiograph, electrocardiogram, complete blood count, basic metabolic panel, and oxygen saturation; arterial blood gas measurements can determine the presence of hypercapnia or hypoxemia.
- **HVC** A sputum culture is not routinely used to assess COPD exacerbations, as it rarely affects management.

Goals and Therapeutic Management

The management goals during an acute COPD exacerbation are to relieve acute symptoms and to prevent future exacerbations. Supplemental oxygen should be used to maintain oxygen saturation between 88% and 92%. Noninvasive positive pressure ventilation may be required if oxygenation or ventilation cannot be maintained. Patients may require intubation and mechanical ventilation if they cannot tolerate NPPV, have an altered mental status, or have worsening hypercapnic or hypoxemic respiratory failure despite the use of NPPV. SABAs with or without anticholinergic agents should be used to relieve acute symptoms. The use of oral glucocorticoids during acute exacerbations has been shown to decrease the frequency of treatment failures, length of stay, and time to subsequent exacerbations while improving FEV_1 and hypoxemia. Glucocorticoids have also been shown to decrease the need for hospitalization if used early. Randomized trials have demonstrated that short courses of lower-dose oral prednisone (40 mg for 5 days) are usually equivalent to longer courses, higher doses, and intravenous administration.

Antibiotics should be prescribed for 5 to 7 days in cases of moderate or severe exacerbations or for patients with mild exacerbations who have noted an increase or change in sputum production. A 2020 systemic review and meta-analysis showed that for mild to severe COPD exacerbations, antibiotics and oral glucocorticoids reduced treatment failure. The most common infectious triggers are viruses, but bacterial causes include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae*. If the patient is still smoking, treatment should also focus on smoking cessation because this can prevent future exacerbations. Because the prevalence of pulmonary embolism is higher in patients with COPD, a thromboembolic event should be considered as a potential trigger if patients do not improve with typical therapies for a COPD exacerbation, and appropriate testing should be performed.

Bronchiectasis

Definition

Bronchiectasis is a chronic suppurative lung disease associated with irreversible enlargement of the airways due to destruction of airway architecture. An injury to the lung typically results in prolonged airway inflammation, which leads to localized injury with subsequent mucus stasis, which can lead to further airway obstruction, chronic infection, and inflammation with worsening bronchiectasis.

Causes

In many cases of bronchiectasis, an underlying cause is not identified. The most common causes of bronchiectasis include cystic fibrosis, aspiration, immunodeficiencies, and connective tissue diseases (**Table 14**).

Presentation

Bronchiectasis should be considered in the differential diagnosis of any patient with a chronic cough, especially if the patient has a history of frequent respiratory infections or if the cough

TABLE 14. Common Causes of Bronchiectasis

Airway obstruction	
	Tumor
	Foreign body
Aspiration	
COPD	
Congenital	
	Mounier-Kuhn syndrome (congenital tracheobronchomegaly)
Autoimmune disorders	
	Rheumatoid arthritis
	Sjögren's syndrome
	Inflammatory bowel disease
Hypersensitivity	
	Allergic bronchopulmonary aspergillosis
Immunodeficiency	
	Common variable immunodeficiency
	HIV
Mucociliary dysfunction	
	Cystic fibrosis
	Primary ciliary dyskinesia
	Young syndrome (bronchiectasis, sinusitis, and obstructive azoospermia and no evidence of cystic fibrosis)
Infection-related	
	Tuberculosis
	Nontuberculous mycobacteria
	Pneumonia, especially recurrent

is productive. Other possible symptoms include hemoptysis, wheezing, and chest pain. Features that should alert the clinician to consider bronchiectasis, especially without significant smoking history, include clubbing and previous sputum cultures growing uncommon pathogens such as *Pseudomonas aeruginosa*, *Aspergillus*, or nontuberculous mycobacteria.

Patients with bronchiectasis may also present with extrapulmonary symptoms, especially fatigue.

Diagnosis

Initial evaluation should include a comprehensive medical history, including childhood diseases, family history, and careful evaluation to exclude known causes of bronchiectasis. Bronchiectasis is diagnosed by high-resolution chest CT. Diagnostic criteria include an airway diameter that is greater than that of its accompanying vessel and lack of distal airway tapering (**Figure 4**). Bronchial wall thickening or cysts may be present. For every diagnosed patient, it should be determined whether there is an underlying cause that can be treated. This may involve testing for chronic bacterial or mycobacterial infections. These tests can identify causes of disease progression and help determine targeted antimicrobial therapy for exacerbations. Patients should also be evaluated for the presence of connective tissue disease and immune function. In selected patients, testing for cystic fibrosis, ciliary dysfunction, or α_1-antitrypsin deficiency may be appropriate. However, even with rigorous evaluation, more than half of all cases are labeled idiopathic.

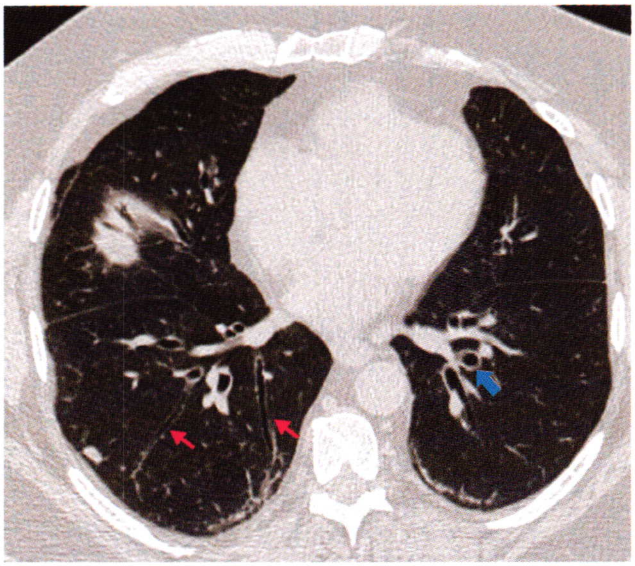


FIGURE 4. Bronchiectasis on chest CT. The airway is larger than its accompanying blood vessel (*thick blue arrow*) and the airway fails to taper distally (*thin red arrows*).

KEY POINTS

- In acute COPD exacerbations, 40 mg prednisone for 5 days has been shown to decrease the frequency of treatment failures, length of stay, and time to subsequent exacerbations while improving FEV_1 and hypoxemia.
- Bronchiectasis is diagnosed by high-resolution chest CT; diagnostic criteria include airway diameter greater than that of its accompanying vessel and lack of distal airway tapering.
- For every patient diagnosed with bronchiectasis, it should be determined whether there is an underlying cause that can be treated.

Treatment

The presence of chronic symptoms of cough and sputum production typically indicates irreversible airway dilation. Therefore, treatment of the underlying cause may not lead to improvement in current symptoms but could prevent further progression. Otherwise, treatment of bronchiectasis focuses on clearing the airway, treating infections, and preventing exacerbations. The goal of airway clearance is to improve mucous clearance and thereby prevent chronic or recurrent infections. Bronchodilators, inhaled glucocorticoids, and combination inhalers have been shown to decrease symptoms but have no effect on the decline of lung function or frequency of exacerbations. Studies suggest that long-term use of macrolide antibiotics may prevent future exacerbations as a result of their anti-inflammatory effects. When deciding whether to use macrolide antibiotics, the risk for future exacerbations should be weighed against the possibility of developing macrolide resistance. Antibiotics may also be used in the management of chronic non-cystic-fibrosis bronchiectasis to eradicate organisms such as *P. aeruginosa* or methicillin-resistant *Staphylococcus aureus*. If eradication of bacterial colonization is not successful, there may be some symptomatic benefit from suppressive therapy with inhaled antibiotics. Patients should also be encouraged to exercise, which can improve airway clearance and symptoms. Surgical resection should be considered in patients who have localized disease with persistent symptoms despite therapy.

KEY POINTS

- Identification and treatment of underlying causes of bronchiectasis should be initiated if possible.
- Treatment of bronchiectasis focuses on clearing the airway, treating infections, and preventing exacerbations.

Treatment of Exacerbations

Exacerbations of bronchiectasis may be difficult to differentiate from baseline symptoms. However, changes in sputum volume, viscosity, or purulence; increased cough; wheezing; shortness of breath; hemoptysis; or declines in lung function are considered evidence of an exacerbation. Therapy for an exacerbation is ideally guided by routine sputum and acid-fast bacilli culture results to identify a possible predominant organism for treatment. Empiric antibiotic therapy is recommended and may be based on previous culture data until the results of the current sputum culture become available. If previous data are not available, a fluoroquinolone can be started to ensure *Pseudomonas* coverage until sputum culture results are available.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease affecting the CF transmembrane conductance regulator (*CFTR*) gene. It is diagnosed in approximately 1 of 2000 to 3000 live births with a predilection for disease in those of European descent. The most common genetic variant resulting in disease is ΔF508, but there are at least 1500 other genetic mutations. The pathogenesis for clinical manifestations of CF remains incompletely understood; however, the abnormal homozygous *CFTR* genotype results in abnormally thick secretions that are difficult to clear. There is an increased concentration of chloride in sweat gland secretions, and sweat chloride testing is a primary diagnostic tool for CF. The changes in respiratory secretions lead to bacterial colonization of airways and chronic bacterial infection, resulting in chronic inflammation and, ultimately, bronchiectasis. Further tissue destruction results from insufficient lung antiproteases to counteract the effect of elastase released from neutrophils. This ongoing inflammatory process also results in large amounts of free DNA and matrix protein deposition within areas of tissue destruction, which further drives increased viscosity of lung secretions.

Thickened secretions in the gastrointestinal tract impair flow of bile and pancreatic secretions, leading to pancreatic exocrine and endocrine deficiency, liver disease, and the development of malabsorption and maldigestion. The secretions increase the risk for bowel obstruction (distal ileal obstructive syndrome, intussusception, and rectal prolapse). As a consequence, individuals with CF often present with malnutrition and weight loss.

Diagnosis

Most patients with CF are diagnosed as children. Adults diagnosed with CF most often present with pulmonary or gastrointestinal symptoms. Pulmonary manifestations often include chronic productive cough, recurrent sinusitis, and recurrent pulmonary infections requiring several courses of antibiotics. For those with gastrointestinal symptoms, loose and frequent stools with abdominal pain are the most common. Pancreatic insufficiency (either endocrine or exocrine) may occur but is less common. Chronic, persistent pulmonary or gastrointestinal symptoms requiring repetitive treatment should raise suspicion for CF. Radiographic findings include hyperinflation followed by bronchiectasis and cyst formation with disease progression, often beginning in the upper lobes.

Often the greatest challenge in diagnosing CF is failing to include it in the differential diagnosis. A family history of CF can be quite helpful in this regard. Sweat chloride testing is the initial test for CF, although it is less sensitive in adults. Abnormal results on repeat testing are diagnostic of CF. Genetic testing confirms the diagnosis and helps with prognosis. A negative sweat chloride test in an adult patient does not rule out disease. Therefore, if the clinical suspicion remains high after negative repeat sweat chloride testing, consideration for referral to a center with expertise in CF or genetic testing is appropriate.

KEY POINTS

- Adults diagnosed with cystic fibrosis most often present with pulmonary or gastrointestinal symptoms; pulmonary manifestations often include chronic productive cough, recurrent sinusitis, and recurrent pulmonary infections requiring several courses of antibiotics.
- A negative sweat chloride test in a patient who presents as an adult should not rule out cystic fibrosis.

Treatment

The pillars of CF management are airway clearance, antibiotic therapy, nutritional support, and psychosocial support. The primary objectives of CF treatment are maintaining lung health and controlling/minimizing the effect of CF-affected organ disease. The Cystic Fibrosis Foundation practice guidelines recommend use of chronic medications to improve lung function and reduce exacerbations. These medications include mucolytics, hydrating agents, inhaled antibiotics, oral macrolide antibiotics, and *CFTR* potentiators. The treatment of CF lung disease is experiencing a period of rapid evolution, and management involves a multidisciplinary approach best provided at a CF care center.

Diffuse Parenchymal Lung Disease

Diffuse parenchymal lung diseases (DPLDs) are a diverse group of nonmalignant disorders resulting in the inflammation and scarring of alveolar structures. These disorders tend to mimic each other clinically and radiographically.

Classification and Epidemiology

Typically, DPLDs are classified into those with a known cause and those that are idiopathic (**Table 15**). This classification has implications for management strategies and prognosis. The prevalence of DPLDs is estimated to be approximately 70 per 100,000 persons.

Diagnostic Approach and Evaluation

The most common presentation of a DPLD is subacute to chronic exertional dyspnea and nonproductive cough. History should include a thorough review of potential exposures,

TABLE 15. Classification of Diffuse Parenchymal Lung Disease

Known Causes	Comments
Drug-induced	Examples: amiodarone, methotrexate, nitrofurantoin, chemotherapeutic agents (see www.pneumotox.com/drug/index for a complete listing)
Smoking-related	Respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia, smoking-related pulmonary fibrosis, combined emphysema with pulmonary fibrosis, pulmonary Langerhans cell histiocytosis
Radiation	Radiation-induced lung injury, radiation pneumonitis/radiation fibrosis; may occur weeks to months after radiation therapy
Chronic aspiration	Aspiration is often subclinical and may exacerbate other forms of DPLD, mainly in the lower lobes; focal consolidation on CT scan of the chest, usually predominantly the right side
Pneumoconioses	Asbestosis, silicosis, berylliosis, coal workers' pneumoconiosis
Connective tissue diseases (RA, systemic sclerosis, dermatomyositis, polymyositis, MCTD, SLE, Sjögren syndrome)	Nonspecific interstitial pneumonia, organizing pneumonia, usual interstitial pneumonia, lymphocytic interstitial pneumonia
Hypersensitivity pneumonitis	Acute, subacute, or chronic
Unknown Causes	**Comments**
Idiopathic interstitial pneumonias	
Idiopathic pulmonary fibrosis	Chronic, insidious onset of cough and dyspnea, usually in a patient aged >50 years; usual interstitial pneumonia pathology (honeycombing, bibasilar infiltrates with fibrosis); diagnosis of exclusion
Idiopathic nonspecific interstitial pneumonia	Affects a younger population than IPF; honeycombing is uncommon on HRCT
Cryptogenic organizing pneumonia	Subacute presentation, patchy opacities that mimic infectious pneumonia
Acute interstitial pneumonia	Rapid progression to respiratory failure; high mortality
Sarcoidosis	Variable clinical presentation, ranging from asymptomatic to multiorgan involvement: stage 1, hilar lymphadenopathy; stage 2, hilar lymphadenopathy plus interstitial lung disease; stage 3, interstitial lung disease; stage 4, fibrosis. Noncaseating granulomas are hallmark.
Rare DPLD With Well-Defined Features	**Comments**
Lymphangioleiomyomatosis	Affects women, usually in their 30s and 40s. Associated with spontaneous pneumothorax and chylous effusions. Chest CT scan shows cystic disease that is diffuse in distribution.
Chronic eosinophilic pneumonia	Chest radiograph shows "radiographic negative" heart failure, with peripheral alveolar infiltrates predominating. Other findings may include peripheral blood eosinophilia and eosinophilia on bronchoalveolar lavage >25%.
Pulmonary alveolar proteinosis	Median age 39 years. Males predominate among smokers, but not nonsmokers. Diagnosed using bronchoalveolar lavage, which shows proteinaceous material in and around alveolar macrophages (periodic acid-Schiff stain positive). Chest CT scan shows "crazy paving" pattern.

DPLD = diffuse parenchymal lung disease; HRCT = high-resolution CT; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MCTD = mixed connective tissue disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

including occupations, home environment, hobbies, and current and past medications, as well as over-the-counter supplements. A history of radiation therapy, a family history of lung disease or connective tissue disease (CTD), and suggestive symptoms of CTD should be explored.

Lung examination findings can range from a normal auscultatory examination to the presence of inspiratory Velcro crackles or an inspiratory squawk suggestive of fibrosis. Extrapulmonary examination findings of associated CTD, such as joint deformities or Gottron papules, may direct the clinician to the cause of the DPLD. Advanced disease may be complicated by pulmonary hypertension and cor pulmonale, with examination findings of jugular venous distention, peripheral edema, and a pronounced pulmonic component of the second heart sound.

It is common for patients with DPLD to have normal resting pulse oximetry. Desaturation of greater than 4% with ambulation is consistent with a diffusion limitation, which is a hallmark of DPLD.

Typically, bilateral diffuse reticular and reticulonodular patterns on chest radiography suggest DPLD. The presence of consolidation, pleural effusions, pleural calcification, bronchiectasis, or lymphadenopathy may provide clues to discrete etiologies for DPLD. Chest radiograph can be normal in patients with minimal disease, and a normal chest radiograph does not rule out DPLD.

Patients for whom a DPLD is suspected should undergo complete pulmonary function testing, including lung volume testing with plethysmography or nitrogen diffusion and DLCO measurement. The vast majority of DPLDs have restrictive physiology, although some diseases may exhibit obstructive or mixed obstructive and restrictive deficits.

KEY POINTS

- The most common presentation of a diffuse parenchymal lung disease is subacute to chronic exertional dyspnea and nonproductive cough.
- Patients with a clinical suspicion of diffuse parenchymal lung disease should undergo complete pulmonary function testing, including lung volumes and DLCO measurement.
- A normal chest radiograph does not rule out DPLD.

High-Resolution CT Scanning

Noncontrast high-resolution CT (HRCT) of the chest is the imaging modality of choice for evaluation of DPLD. Distribution of disease and pattern of pulmonary parenchyma involvement may suggest the underlying diagnosis (**Table 16**). Addition of

TABLE 16. Patterns of Disease Associated With a Diagnosis of Diffuse Parenchymal Lung Disease

Lung Disease	Imaging	Comments
Acute interstitial pneumonia	Diffuse ground glass with consolidation	Indistinguishable from ARDS but without a risk factor for ARDS
Organizing pneumonia	Patchy ground glass, alveolar consolidation, peripheral and basal predominance	Connective tissue diseases, infections, drug-related, or idiopathic
Idiopathic pulmonary fibrosis/usual interstitial pneumonia	Basal-predominant and peripheral-predominant septal line thickening with traction bronchiectasis and honeycomb changes	Usual interstitial pneumonia pattern can be seen in connective tissue disease, asbestosis, and chronic hypersensitivity pneumonitis; idiopathic pulmonary fibrosis is diagnosis of exclusion
Nonspecific interstitial pneumonia	Ground glass, basal predominance	Idiopathic and common finding in connective tissue disease
Respiratory bronchiolitis	Centrilobular nodules and ground-glass opacity in an upper-lung-predominant distribution	May be an asymptomatic finding in an active smoker
Desquamative interstitial pneumonia	Basal-predominant and peripheral-predominant ground-glass opacity with occasional cysts	Most cases are smoking related; chest radiograph may be normal in 20%, but HRCT demonstrates ground-glass opacities
Hypersensitivity pneumonitis	Acute: ground-glass opacification; centrilobular micronodules that are upper- and mid-lung-predominant Chronic: mid-lung- and upper-lung-predominant septal lung thickening with traction bronchiectasis; usual interstitial pneumonia pattern may be seen	Acute: associated with flulike illness Chronic: often cannot identify a causative antigen
Sarcoidosis	Upper-lobe-predominant; mediastinal and hilar lymphadenopathy; cystic changes, including development of aspergilloma; small nodules oriented along bronchovascular bundles	Findings for sarcoidosis often not specific; DPLD with diffuse mediastinal and hilar lymphadenopathy greater than 2 cm in size should raise suspicion

ARDS = acute respiratory distress syndrome; DPLD = diffuse parenchymal lung disease; HRCT = high-resolution CT scan.

expiratory images to accentuate air trapping can elucidate small airways disease. Prone images may be helpful to distinguish subpleural reticular opacities and septal thickening from dependent atelectasis.

Serologic Testing

For patients with newly detected DPLD of apparently unknown cause who are clinically suspected of having idiopathic pulmonary fibrosis, the American Thoracic Society guidelines recommend serologic testing to exclude CTD-associated DPLD. Routine testing with C-reactive protein, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, myositis panel, and anti–cyclic citrullinated peptide antibodies is recommended. See MKSAP 19 Rheumatology for further discussion of testing for connective tissue disease.

Lung Biopsy

When pulmonary function tests and HRCT are insufficient for making the diagnosis, the physician must consider a bronchoscopic or surgical lung biopsy. Careful assessment of risk factors, alternate diagnostic strategies, and effect of the results of lung biopsy on treatment should be discussed within a multidisciplinary team, including a thoracic radiologist, thoracic surgeon, and pulmonary specialist with expertise in DPLD.

KEY POINT

- Noncontrast high-resolution CT scan of the chest is the imaging modality of choice for evaluation of diffuse parenchymal lung disease.

Diffuse Parenchymal Lung Diseases With a Known Cause

Smoking-Related Diffuse Parenchymal Lung Disease

DPLDs that occur almost exclusively in individuals who are current smokers include respiratory bronchiolitis-associated interstitial lung disease (RB-ILD); desquamative interstitial pneumonia (DIP), a more severe form of smoking-related DPLD; pulmonary Langerhans cell histiocytosis (PLCH); and smoking-related interstitial fibrosis (SRIF). Smoking in conjunction with other endogenous or exogenous factors may also contribute to IPF as well as combined pulmonary fibrosis and emphysema.

Typical findings on HRCT include ground-glass opacities with fine centrilobular nodules in RB-ILD, diffuse ground-glass opacification with lower zone predominance in DIP, and diffuse thin-walled cysts and nodular lesions in upper and mid lung zones in PLCH. Patients with PLCH also have a predilection to recurrent pneumothoraces. Demonstrating abnormal numbers of Langerhans cells with S100 or CD1a staining in bronchoalveolar lavage fluid or on tissue obtained by either transbronchial or open lung biopsy confirms the diagnosis.

SRIF is an entity that radiologically mimics RB-ILD. However, it is pathologically distinct, with deposition of hyalinized collagen in alveolar septa and minimal inflammation.

On physiologic testing, patients with any smoking-related DPLD will have a reduced DLCO. RB-ILD and SRIF may have combined restriction and obstruction, whereas DIP typically is associated with pure restrictive disease. PLCH often produces restrictive disease but may have preserved total lung capacity and evidence of obstruction when significant cystic disease is present. COPD is a common comorbidity that may add an obstructive component to testing in any patient who smokes.

For all smoking-related DPLDs, the primary management is smoking cessation. Glucocorticoids may be considered with severe disease or in those with refractory symptoms.

KEY POINT

- The primary management of all smoking-related DPLDs is smoking cessation.

Connective Tissue Diseases

Immune-mediated injury from underlying connective tissue disease can result in DPLD. Typically manifesting in patients with an established CTD, lung disease can occasionally arise before the development of extrapulmonary findings. Younger patients who present with DPLD have a higher prevalence of CTD. CTD-related DPLDs encompass all major HRCT patterns of DPLD (**Table 17**). Nonspecific interstitial pneumonia is more common than usual interstitial pneumonia (UIP) in patients with CTD. Furthermore, patients with CTD treated with doses of methotrexate greater than 15 mg/wk, and sometimes other agents, may be at risk for drug-induced DPLD.

One syndrome in patients with CTD–ILD that warrants particular attention is the antisynthetase syndrome. This syndrome presents as polymyositis or dermatomyositis with radiographic evidence of ILD in combination with one or more anti-aminoacyl-tRNA synthetase antibodies. Patients may not have overt signs of systemic disease; however, ILD may be severe and rapidly progressive. See MKSAP 19 Rheumatology for further discussion of antisynthetase syndrome.

Glucocorticoids and immunomodulatory therapy with agents such as mycophenolate mofetil, methotrexate, cyclophosphamide, and rituximab may be used in consultation with rheumatology and pulmonary specialists.

Hypersensitivity Pneumonitis

Repetitive inhalation of specific antigens in a sensitized patient can result in hypersensitivity pneumonitis (HP), an immunologic response that results in noncaseating granulomas and peribronchial mononuclear cell and giant cell inflammation. The antigens are typically complex proteins that can come from several sources, including agricultural dusts, thermophilic fungi, and bacteria, but they can also be low-molecular-weight organic compounds. There are three forms of HP, and each presents differently. The acute form, which is the most easily identified form, results after a large exposure to an inciting antigen. The patient typically develops fever, cough, and fatigue within 12 hours of exposure. Chest radiography can demonstrate diffuse micronodular

TABLE 17. Connective Tissue Diseases Associated With Diffuse Parenchymal Lung Disease

Connective Tissue Disease	Typical DPLD Patterns and Associated Pulmonary Manifestations
Rheumatoid arthritis	Usual interstitial pneumonia Nonspecific interstitial pneumonia Organizing pneumonia Rheumatoid nodules Other pulmonary manifestations: pleuritis and pleural effusion, airway disease
Systemic sclerosis	Nonspecific interstitial pneumonia Other pulmonary manifestations: pulmonary hypertension, aspiration from esophageal dysmotility
Polymyositis/dermatomyositis	Nonspecific interstitial pneumonia Organizing pneumonia
Systemic lupus erythematosus	Nonspecific interstitial pneumonia Organizing pneumonia Lymphocytic interstitial pneumonia Other pulmonary manifestations: acute pneumonitis, pulmonary hemorrhage, pleuritis, thromboembolic disease, pulmonary hypertension, shrinking lung syndrome
Sjögren syndrome	Nonspecific interstitial pneumonia Lymphocytic interstitial pneumonia
Mixed connective tissue disease	Nonspecific interstitial pneumonia Organizing pneumonia
ANCA-associated vasculitis	Usual interstitial pneumonia Less commonly, nonspecific interstitial pneumonia

ANCA = antineutrophil cytoplasmic antibody; DPLD = diffuse parenchymal lung disease.

disease but may be normal. Physical examination will reveal inspiratory crackles. If HRCT is performed, it will demonstrate diffuse centrilobular micronodules and ground-glass opacities (**Figure 5**). After removal from the offending antigen, symptoms usually resolve within approximately 48 hours. Recurrence of symptoms if the patient is rechallenged is the hallmark of the disease.

Subacute and chronic forms of HP occur after more prolonged lower-level antigen exposure. "Bird fancier's lung disease" is an example of a chronic disorder caused by inhalation of avian proteins from feathers, skin, or guano. These patients experience cough, fatigue, weight loss, and shortness of breath. As in the acute form, the HRCT scan will show micronodules and ground-glass opacities, but there is also evidence of septal thickening and fibrosis. In the disease's most severe and chronic form, significant traction bronchiectasis and honeycomb changes will be evident. Evidence of severe fibrosis on CT imaging significantly increases the risk for disease progression and death.

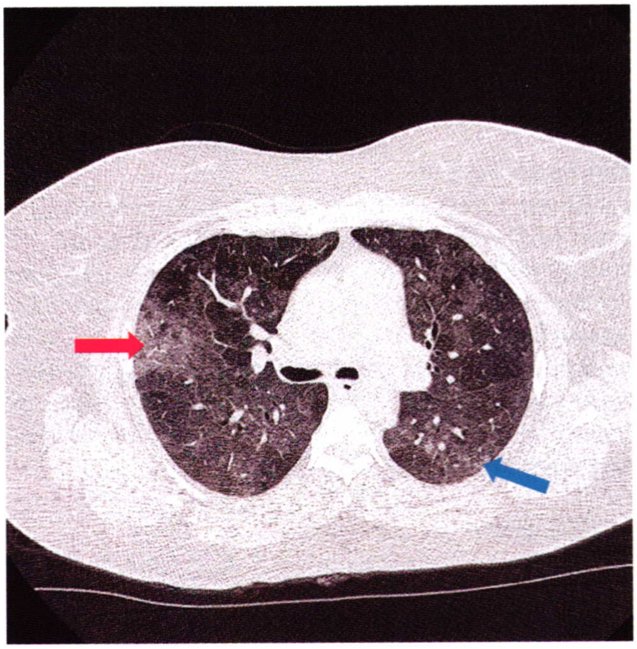


FIGURE 5. Chest CT scan demonstrating hypersensitivity pneumonitis with patchy, bilateral ground-glass opacities (*red arrow*) and centrilobular micronodules (*blue arrow*) in the midlung section.

Removal of exposure to the offending antigen is essential in the treatment of HP. To identify potential antigens, a careful history is vital, as serologic testing is often limited and may not include antibodies to the responsible antigen. Glucocorticoids and sometimes other immunosuppressants are often used for those with more severe symptoms.

KEY POINT

- Removal of exposure to the offending antigen is essential in the treatment of hypersensitivity pneumonitis.

Drug-Induced Diffuse Parenchymal Lung Disease

Many medications have been implicated in the development of DPLD (**Table 18**). Duration of exposure to the development of disease can vary, even for the same agent. For instance, amiodarone lung toxicity has an acute form presenting with acute lung injury/acute respiratory distress syndrome, as well as a chronic indolent form with reticular abnormalities and subpleural nodules. Prompt treatment by removal of the offending agent is important for resolution of symptoms. For those with more severe symptoms, glucocorticoids may have some benefit, although data are anecdotal.

Radiation Pneumonitis

Radiation pneumonitis typically occurs 4 to 12 weeks after radiation exposure. Patients present with cough, shortness of breath, and radiographic infiltrates. Fever, pleuritic chest pain, fatigue, and weight loss are accompanying nonspecific symptoms. Differential diagnosis often includes infection and drug-induced lung injury. On imaging, a well-defined nonanatomic demarcation between normal and abnormal lung consistent

TABLE 18. Selected Drug-Induced Parenchymal Lung Diseases

Drug	Clinical Points	Radiographic Findings and Treatment
Amiodarone	More common in: Older patients Increased dosage and higher cumulative dose First year of therapy (but can occur late)	Multiple radiographic presentations possible, including ground-glass opacities, subpleural nodules, and reticular abnormalities Very long half-life prevents clearance from the pulmonary parenchyma: Rare improvement with discontinuation of the drug alone High risk for recurrence with tapering of glucocorticoids
Methotrexate	Occurs in less than 5% of treated patients Unpredictable time to presentation No clear correlation between dose and disease severity	Diffuse reticular and ground-glass attenuation Patients generally do well after stopping medication Glucocorticoids are often given; duration is based on response
Nitrofurantoin	Acute (more common): Fevers, chills, cough, shortness of breath, chest pain; rash can occur in 10%-20% of patients Peripheral eosinophilia common Chronic: Distinct from the acute form Onset months to years after prolonged exposure	Acute: Faint bilateral lower lobe septal lines; moderate pleural effusions may be present; often resolves with discontinuation but will recur with repeat exposure Chronic: Reticular opacities with subpleural lines and thickened peri-bronchovascular areas; possible benefit of glucocorticoids from anecdotal reports
Busulfan	Occurs in less than 8% of treated patients Currently used solely as a preparative regimen for HSCT; often combined with other agents associated with pulmonary toxicity Injury typically occurs 30 days to 1 year after exposure	Multiple patterns, including ground-glass opacities, reticulation, bibasilar septal lines, asymmetric peripheral and peribronchial consolidation, centrilobular nodules, and dependent consolidation Optimal treatment unknown and is often supportive Glucocorticoids may be used for more progressive disease
Bleomycin	Risk significantly increases with cumulative dose Increased age, kidney disease, concomitant chemotherapy or irradiation also increase risk for toxicity Typically subacute presentation 1-6 months after exposure; may show hypersensitivity pneumonitis, diffuse alveolar damage, or usual interstitial pneumonia pathologically but with more rapid clinical onset and progressive course	Imaging patterns suggest the multiple possible pathologic findings seen: Consolidation with ground glass (diffuse alveolar damage) Septal line thickening, traction bronchiectasis, and honeycomb change (end-stage fibrosis) Patchy ground glass with subpleural consolidation or peribronchial consolidation (organizing pneumonia) Diffuse ground glass with centrilobular micronodules (hypersensitivity pneumonitis) Glucocorticoids used for more severe disease; disease may recur with tapering of steroids

HSCT = hematopoietic stem cell transplantation.

with the radiation field is pathognomonic but not always present. Other lung abnormalities, such as organizing pneumonia, may also be observed outside the field of exposure. Observation may be appropriate for those with mild disease. Glucocorticoids are used for patients with severe symptoms or hypoxemia. From 6 to 12 months after radiation exposure, additional findings on HRCT may develop, including septal thickening, traction bronchiectasis, and volume loss consistent with chronic fibrosis. Individuals exposed to radiation are also at risk for the development of radiation recall pneumonitis, which can occur when lung tissue is subsequently exposed to certain immune checkpoint inhibitors and chemotherapy agents, including doxorubicin, etoposide, gemcitabine, paclitaxel, and pemetrexed, which trigger pathologic changes in the lung tissue previously exposed to radiation.

KEY POINTS

- Radiation pneumonitis typically presents 4 to 12 weeks after initial radiation exposure with cough, shortness of breath, and a new radiographic infiltrate.
- Treatment of severe forms of radiation pneumonitis typically is glucocorticoids, whereas observation may be appropriate for those with mild disease.

Diffuse Parenchymal Lung Diseases With an Unknown Cause

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), which is associated with the histopathologic pattern of UIP, is the most common idiopathic form of DPLD. Deemed to be a reflection of dysregulated fibrosis in response to alveolar epithelial injury, it typically presents with chronic cough and dyspnea in patients between 50 and 70 years of age. Lung examination is notable for bibasilar Velcro-like inspiratory crackles. Clubbing is present in up to 50% of patients. Smoking is considered a risk factor, and patients are often treated for COPD without significant improvement. Chest radiographs may demonstrate bibasilar reticular changes. Characteristic HRCT abnormalities include bilateral, subpleural, and basal predominant reticular changes. Advanced cases may develop traction bronchiectasis with subpleural clusters of palisading cysts called honeycombing (**Figure 6**). When HRCT findings are classic for UIP, lung biopsy is not necessary for diagnosis.

IPF is progressive, with a median survival of 3 to 5 years after diagnosis. Patients may experience acute exacerbations with a rapid worsening of symptoms and development of bilateral ground-glass opacities superimposed on areas of background fibrosis. These events may represent an acceleration of the disease. Even though glucocorticoids and antibiotics are frequently used, there are no proven therapies for acute exacerbations of IPF.

Management of patients with IPF should include consideration of antifibrotic therapies and oxygen supplementation for hypoxemia. In 2014 the FDA approved nintedanib, a tyrosine kinase inhibitor, and pirfenidone, an antifibrotic agent, for use in patients with IPF. Although the mechanisms of these two medications differ, the clinical response is quite similar, with both demonstrating a decline in the rate of progression of disease. Although these medications delay IPF progression, they are not curative. Referral to a pulmonologist or ILD center is appropriate before initiating treatment with these medications.

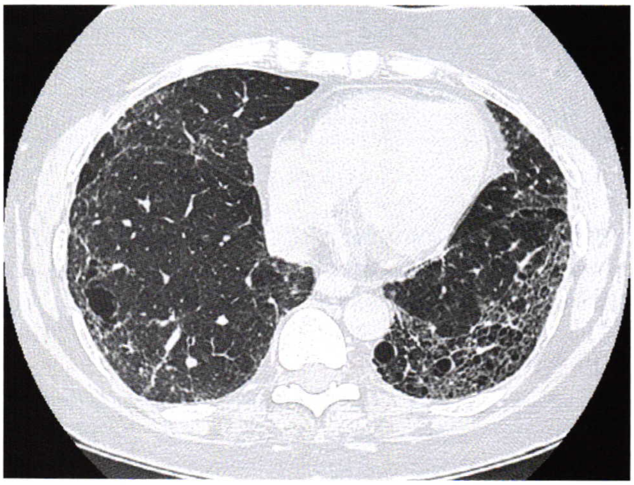


FIGURE 6. High-resolution chest CT scan demonstrating the typical findings in idiopathic pulmonary fibrosis, including increased reticular changes that are predominantly peripheral and basilar in distribution, honeycombing (at the left base), and absence of significant ground-glass opacification.

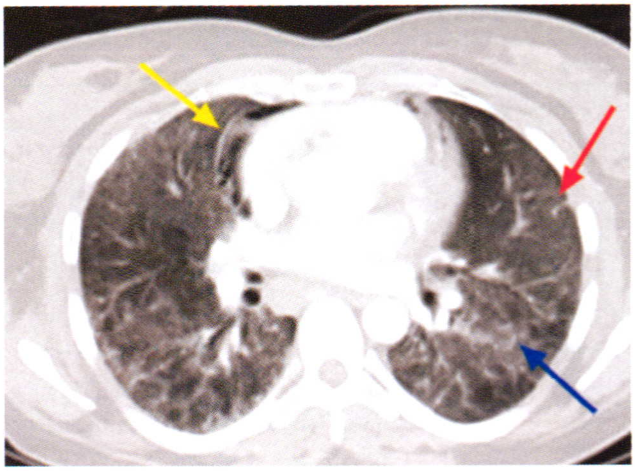


FIGURE 7. Chest CT scan demonstrating nonspecific interstitial pneumonia with scattered bilateral ground-glass opacities (*blue arrow*) and areas of subpleural sparing (*red arrow*) in the lower lung section. Also noted incidentally is trace pneumomediastinum (*yellow arrow*) on the right lung.

Given the progressive and unpredictable clinical course of IPF, early referral to a lung transplant center is strongly recommended.

Palliative care consultation to establish advanced care plans should be considered for patients with IPF who are not candidates for lung transplantation.

KEY POINTS

- When high-resolution CT findings are classic for usual interstitial pneumonia, lung biopsy is not necessary for diagnosis. **HVC**
- Therapy with nintedanib and pirfenidone decreases the rate of progression of idiopathic pulmonary fibrosis but is not curative.

Nonspecific Interstitial Pneumonia

Although nonspecific interstitial pneumonia (NSIP) is a common variant in CTD-associated DPLD, idiopathic NSIP is a distinct clinical entity. Differentiation of idiopathic NSIP from IPF is critical as the two diseases have distinct treatment algorithms and IPF has a worse prognosis. NSIP typically affects a younger population than IPF. The HRCT scan typically demonstrates bilateral lower-lobe reticular changes and scattered ground-glass opacities (**Figure 7**). Although NSIP can progress to fibrosis, honeycombing, which is a classic feature for UIP, is rarely seen in NSIP. Biopsy is frequently warranted to confirm the diagnosis and exclude alternate pathologies and may reveal inflammation and fibrosis. On the basis of the extent of inflammation and fibrosis, cellular and fibrotic forms of NSIP are described. The cellular form has a better prognosis and typically responds to immunosuppressive treatments. Although the overall prognosis is better than for IPF, the 5-year mortality of idiopathic NSIP remains approximately 15% to 25%. As with IPF, selected patients may benefit from lung transplantation.

KEY POINT

- On high-resolution CT, nonspecific interstitial pneumonia typically demonstrates bilateral lower-lobe reticular changes and areas of ground-glass opacification.

Cryptogenic Organizing Pneumonia

Organizing pneumonia is defined by histopathologic findings of patchy proliferation of granulation tissue that affects the terminal bronchioles and alveolar ducts and spaces and is associated with surrounding inflammation. This pattern is nonspecific and often follows or is associated with various types of injury to the lung, including acute infection, radiation exposure, drug-induced pneumonitis, and autoimmune diseases. In patients in whom no cause is identified, the diagnosis is termed cryptogenic organizing pneumonia (COP).

Patients with COP typically have a subacute presentation with cough, fever, and malaise over weeks to months. Initial chest radiographs typically demonstrate patchy opacities that mimic pneumonia, and as a result, patients are often initially misdiagnosed with pneumonia and treated with antibiotics (**Figure 8**). However, nonresolving symptoms and failure to respond to antibiotics should raise suspicion for organizing pneumonia or COP. HRCT findings can range from ground-glass opacities to areas of alveolar consolidation resembling an infectious pneumonia. The diagnosis may not require lung biopsy if the clinical presentation and HRCT findings are consistent with COP. For cases with atypical presentation, lung biopsy helps make the diagnosis.

Patients with COP respond well to glucocorticoid therapy. Relapses of COP with tapering of glucocorticoids are common. In such settings, consideration of glucocorticoid-sparing therapies is warranted.

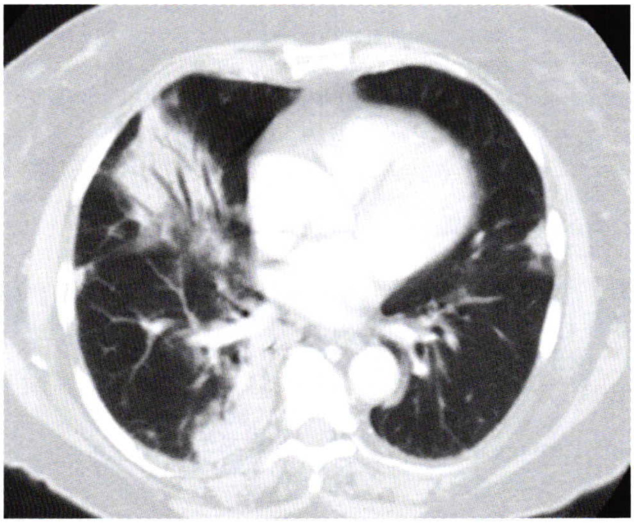


FIGURE 8. Chest CT scan demonstrating bilateral patchy opacities with air bronchograms mimicking pneumonia. Transbronchial biopsies from right middle lobe revealed organizing pneumonia and opacities resolved with oral glucocorticoids.

KEY POINTS

- Cryptogenic organizing pneumonia typically presents as cough, fever, and malaise lasting weeks to months, and imaging findings mimic infectious pneumonia; treatment is with glucocorticoids.
- The diagnosis of cryptogenic organizing pneumonia (COP) may not require lung biopsy if the clinical presentation and high-resolution CT findings are consistent with COP; for cases with atypical presentation, lung biopsy helps make the diagnosis. **HVC**

Acute Interstitial Pneumonia

Acute interstitial pneumonia develops rapidly over days to weeks, resulting in acute respiratory failure with bilateral alveolar opacities on HRCT of the chest. The pathologic findings on open lung biopsy are those of diffuse alveolar damage. This process is clinically, radiographically, and pathologically indistinguishable from acute respiratory distress syndrome (ARDS). The absence of known risk factors for the development of ARDS suggests a diagnosis of acute interstitial pneumonia.

Management includes ventilatory support and critical care, as it does for patients with ARDS. Mortality remains high (approximately 50%), and those who recover from the initial illness often have complications, are at risk for the development of chronic lung disease, and may have a relapse. Patients are often treated with high-dose glucocorticoids, although strong evidence to support their use is lacking.

KEY POINT

- Acute interstitial pneumonia is clinically, radiographically, and pathologically indistinguishable from acute respiratory distress syndrome (ARDS), but patients lack risk factors for ARDS.

Combined Pulmonary Fibrosis and Emphysema

Combined pulmonary fibrosis and emphysema (CPFE) is a distinct clinical entity wherein fibrotic lung disease, similar to IPF, coexists with emphysematous changes in the same patient (**Figure 9**). Even with advanced architectural changes, lung function studies may reveal preserved spirometry and lung volumes. Marked impairment in gas exchange manifesting as reduced diffusing capacity is typical for CPFE. Presence of pulmonary hypertension in patients with CPFE portends a poor prognosis. Lung transplant is the only curative therapy.

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown cause that can affect any organ system. More than 90% of patients with sarcoidosis have lung involvement. The prevalence of sarcoidosis is approximately 10 to 20 per 100,000 individuals. Sarcoidosis affects Black persons more frequently than White persons and typically occurs in younger patients. Many

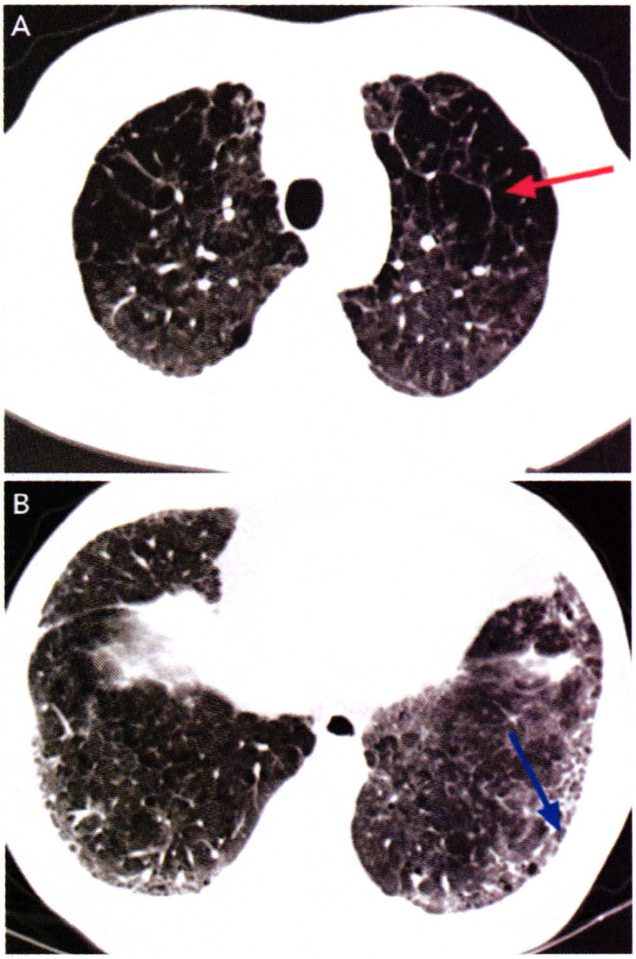


FIGURE 9. Representative chest CT scan cuts demonstrating combined pulmonary fibrosis and emphysema, with upper lobe emphysema (*A; red arrow*) and lower lobe subpleural reticular and fibrotic changes (*B; blue arrow*).

patients are asymptomatic, and lung involvement is incidentally found on chest radiography performed for other reasons (**Figure 10**). Findings from chest radiography can help predict the probability of spontaneous resolution (**Table 19**). CT scanning can show pulmonary parenchymal disease or intrathoracic lymphadenopathy, either alone or in combination. Presence of nodules along bronchovascular bundles on HRCT imaging suggests sarcoidosis as the cause of the disease.

Pulmonary function testing is typically abnormal and findings can be obstructive, restrictive, or both. Sarcoidosis is a diagnosis of exclusion. Diagnosis, with a few exceptions (**Table 20**), typically requires bronchoscopic biopsy, with tissue obtained from a lymph node or from the pulmonary parenchyma. The diagnosis is made by the finding of noncaseating granulomas with exclusion of potential mimicking infections (mycobacteria, fungi), exclusion of other systemic granulomatous diseases, and ideally involvement of more than one organ system.

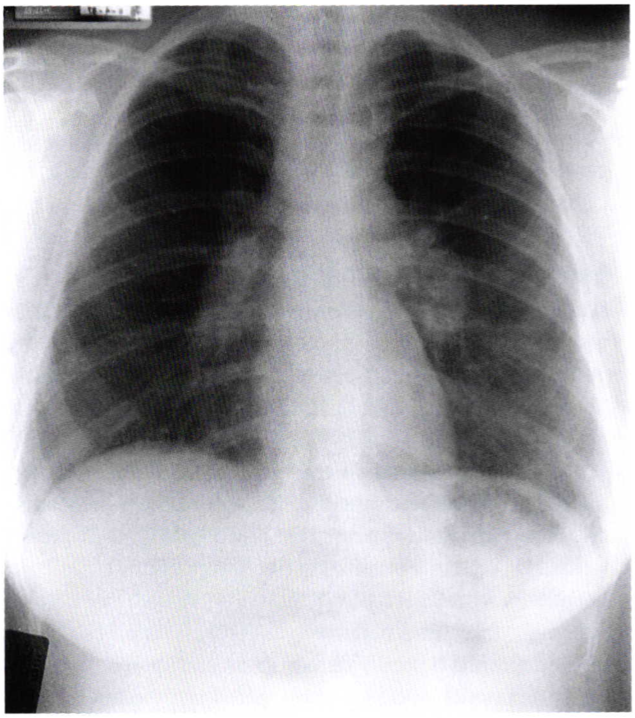


FIGURE 10. Chest radiograph showing stage I pulmonary sarcoidosis with hilar lymphadenopathy and normal lung parenchyma.

Development of pulmonary hypertension in patients with sarcoidosis is a poor prognostic indicator, with a median survival of approximately 3 years.

The primary treatment of sarcoidosis is glucocorticoids, although many patients do not need to be treated. In addition, spontaneous resolution without treatment is common and is related to the radiographic stage of disease (see Table 19). The decision to treat and assessment of response to treatment should be based on symptoms and organ dysfunction, not radiographic findings. For those without symptoms or organ

TABLE 19. Chest Radiograph Staging of Pulmonary Sarcoidosis

Stage	Radiographic Pattern	Clinical Course and Comments
0	Normal	
I	Hilar lymphadenopathy with normal lung parenchyma	>90% rate of spontaneous resolution without treatment
II	Hilar lymphadenopathy with abnormal lung parenchyma	Approximately 50% rate of spontaneous improvement without treatment
III	No lymphadenopathy with abnormal lung parenchyma	Approximately 20% rate of spontaneous improvement without treatment
IV	Parenchymal changes with fibrosis and architectural distortion	

TABLE 20. Clinical Presentations of Sarcoidosis That Do Not Require a Biopsy

Syndrome	Additional Findings/Symptoms
Asymptomatic bilateral hilar lymphadenopathy	No evidence of fevers, malaise, or night sweats to suggest a malignancy
Löfgren syndrome	Bilateral hilar lymphadenopathy, migratory polyarthralgia, erythema nodosum, and fever
Heerfordt syndrome	Anterior uveitis, parotitis, fever (uveoparotid fever), and facial nerve palsy

dysfunction, observation is appropriate. If treatment is required, glucocorticoid therapy is appropriate. For patients with more severe or prolonged symptoms, adverse effects from chronic glucocorticoids should be considered. In this setting, adjunctive glucocorticoid-sparing therapies are often used. Pulmonary consultation should be considered for management of persistent disease. For patients with pulmonary hypertension or severe disease with significant activity limitation resulting from lung impairment, evaluation for lung transplantation is appropriate.

For nonpulmonary manifestations of sarcoidosis, see MKSAP 19 Rheumatology.

KEY POINTS

- More than 90% of patients with sarcoidosis have lung involvement; radiographic staging can predict the probability of spontaneous resolution.
- The primary treatment of symptomatic sarcoidosis is glucocorticoids, often followed by glucocorticoid-sparing therapies.
- Löfgren syndrome consists of erythema nodosum, arthritis, fever, and hilar lymphadenopathy; a biopsy is not needed to confirm the diagnosis.

Occupational Lung Disease

When to Suspect an Occupational Lung Disease

Occupational lung disease can affect any part of the respiratory tract, including sinuses, airways, the lung parenchyma, and the surrounding pleura. As a result, signs and symptoms associated with occupational exposure include rhinitis, reactive airways disease, reactive airways dysfunction syndrome (see Airways Disease section), COPD, pleural disease, diffuse parenchymal lung disease, and malignancy. Occupational lung diseases can present acutely, subacutely, or slowly after many years of exposure. Therefore, a careful employment history that includes occupational exposures is essential for diagnosis (**Table 21**). Clinical presentations related to silica and asbestos exposures are well characterized and recognized. However, new agents that may lead to respiratory diseases are frequently introduced in various industries. Factors suggesting an underlying occupational lung disease include patient concerns about an exposure, a temporal association with an exposure, unexplained signs or symptoms, and evidence of coworkers with similar symptoms. In addition, patients may experience relief of symptoms when away from the work environment and recurrence of symptoms on their return. For the patient with occupational lung disease, similar to those with diffuse parenchymal lung disease, cough and dyspnea on exertion are common.

TABLE 21. Occupational Lung Disease Screening Questionnaire

Occupation
What do you do every day at your job?
Have you always done these tasks at work?
Have you had other duties?
How long have you been working in this job? Have you had a similar job elsewhere?
What other types of work have you done?[a]
Type and Extent of Exposure
Describe your work area. Is there adequate ventilation? Is there visible dust in the air? Is visibility across the work area limited because of the amount of dust in the air?
Are you exposed to vapors, gases, dust, or fumes in your work?
Does your employer require you to wear personal protective equipment? If so, do you wear it for the full extent of your exposure?
Do you know the amount and type of chemicals used?
Do you have Safety Data Sheets from your workplace?
Temporal Relationship of Symptoms to the Work Environment
Before symptoms began, were there any changes in the processes at work or new exposures?
When you are off work, do your symptoms improve?
Are there others at work who have developed similar symptoms?
Has a process change at work resulted in improved symptoms?
Other Relevant Exposures
Do you perform activities at home that may expose you to organic or inorganic dust (for example, refurbishing old cars or woodworking)?
Do you have any pet birds at home? Do you have any pets?
Have you always lived in the area?
Have you traveled recently?

[a] Obtain a full accounting of other jobs.

Key Elements of the Exposure History

The time course from exposure to the development of signs and symptoms of occupational lung disease is highly variable.

TABLE 22. Key Features of Occupational Lung Diseases

Occupational Pulmonary Disease	Key Features
Airways diseases	
Work-related asthma (occupation-related asthma)	Key is to diagnose airways disease in conjunction with exposure. Preshift and postshift spirometry, serial peak flow measurements, methacholine challenge test, inhalational challenge test; serologic tests for specific antigens.
Occupational COPD	Pulmonary function tests showing obstruction; may develop in nonsmokers also.
Diffuse parenchymal lung diseases	High-resolution CT is the imaging modality of choice. Pulmonary function tests show mixed restrictive and obstructive physiology.
Dust-related pneumoconiosis	
Silica (acute silicosis, chronic simple silicosis, chronic complicated silicosis, accelerated silicosis)	Silica exposure in industries that cut or grind silica-containing materials, sandblasting, hydraulic fracking for natural gas. Silica exposure associated with increased risk for tuberculosis and autoimmune diseases. Imaging shows ground-glass, nodular, interstitial, or fibrotic infiltrates.
Coal (simple or complicated coal-worker's pneumoconiosis)	Less common today given improved mine safety standards. Imaging shows nodular or fibrotic changes.
Asbestos-related pleuropulmonary disease	Long latency (>25 years) from exposure to onset. Amphibole asbestos more pathogenic than serpentine asbestos. Pulmonary fibrosis and pleural disease (effusions, plaques, pleural thickening).
Metal-induced lung disease	Cobalt: giant cell interstitial pneumonitis. Indium: pulmonary alveolar proteinosis. Imaging shows ground-glass opacities.
Occupational hypersensitivity pneumonitis	Typically acute or subacute in the occupational setting.
Chronic beryllium disease (CBD)	Beryllium use in aerospace, automotive, nuclear, and telecommunication industries. Exposure in a patient with a granulomatous lung disease should prompt consideration of CBD. Diagnosed by beryllium lymphocyte proliferation test.
Lung malignancies	Lung cancer (histologic subtypes vary with type of exposure), mesothelioma (strongly associated with asbestos exposure).

Exposures within the same industry can vary according to use of best practices and the type of workplace. For example, coal worker's pneumoconiosis in the United States has substantially decreased since the institution of federal safety standards. However, rates of coal worker's pneumoconiosis are higher for individuals who work for companies with fewer than 50 employees and for those who work in thin-seam mines. Thin-seam mines appear to have higher crystalline silica exposure and pose greater risk. Adequate determination of exposure requires a clear description of job duties and determination of the extent of dust exposure. Clinicians should also obtain a history of additional exposures from hobbies and the home environment (see Table 21). Key features of the more frequently encountered occupational lung diseases are summarized in **Table 22**.

When an occupational lung disease is suspected, clinicians should request a Safety Data Sheet from the patient's employer; the Safety Data Sheet details chemical properties and known health risks associated with substances within the workplace. The U.S. Occupational Safety and Health Administration requires that employers make this information available on request for employees who work with potentially harmful materials.

For individuals who have undiagnosed disorders, persistent unexplained symptoms, or permanent impairment possibly due to an occupational lung disease, referral to an occupational or environmental lung disease specialist is appropriate.

KEY POINTS

- Presentations of occupational lung disease include rhinitis, reactive airways disease, reactive airways dysfunction syndrome, COPD, pleural disease, diffuse parenchymal lung disease, or malignancy.
- When an occupational lung disease is suspected, it is essential to obtain a complete history, including occupation, type and extent of exposure, temporal relationship of exposure to symptoms and disease, and other exposures at home and from hobbies.

Management

The key to management of occupational lung disease is removal of the offending agent from the workplace or the worker from the offending agent. Further investigation of the workplace to ensure the identification of all affected individuals is essential.

Workers' compensation and determination of disability related to the impairment attributed to occupational exposure may require referral to a specialist with expertise in occupational lung disease.

KEY POINT

- The key to management of occupational lung disease is removal of the offending agent from the workplace or the worker from the offending agent; further investigation of the workplace to ensure the identification of all affected individuals is essential.

Surveillance

For individuals at high risk for the development of pulmonary disease, the use of health questionnaires and pulmonary function screening is appropriate; such screening can also identify a new exposure and any associated risk for disease development. Surveillance systems that catalog sentinel cases of disease can help identify clustering of cases. A major limitation of these databases is the failure of physicians to report events.

Pleural Disease

The pleural space is the space between the visceral and parietal pleura, which cover the lung and the chest wall, respectively. The physiologic function of this space is not well understood, but it has been suggested that it helps maintain positive transpulmonary pressure, which prevents atelectasis. The two main abnormalities affecting the pleura result from the presence of either excess fluid (pleural effusion) or excess air (pneumothorax) in the pleural space.

Pleural Effusion

Each year more than 1.5 million new cases of pleural effusion are diagnosed in the United States. Most effusions are benign; however, approximately 16% are secondary to malignancy. Heart failure, pneumonia, and malignancy are the most common etiologies in the United States. Normally the pleural space contains only a small amount of fluid (less than 15 mL). Pleural effusions result from conditions that affect the rate of fluid entry from pleural capillaries and the ability of lymphatics to absorb the fluid.

KEY POINT

- Heart failure, pneumonia, and malignancy are the most common causes of pleural effusion in the United States.

Evaluation

History and Physical Examination

The cause of a pleural effusion is often suggested by patient history and physical examination. Symptoms typically include dyspnea, cough, and pleuritic chest pain. Elderly patients often present with atypical symptoms such as anemia, fatigue, and failure to thrive. Key questions include severity and duration of symptoms; constitutional symptoms such as fevers, night sweats, and weight loss; occupation; recent illness, injury, or travel; exposures (for example, asbestos); and medical history such as heart failure, previous surgeries, and medications. The chest examination may reveal dullness to percussion and diminished or absent fremitus and breath sounds if the effusion is larger than 300 mL. There are several other key physical examination findings that may suggest the cause of the effusion (**Table 23**).

TABLE 23. Key Physical Examination Findings in the Evaluation of a Pleural Effusion

Finding	Possible Causes of Pleural Effusion
Distended neck veins, S_3 gallop, pulmonary crackles	Heart failure
Bilateral dependent edema	Heart failure, nephrotic syndrome, cirrhosis, hypoalbuminemia
Calf or thigh swelling, erythema, edema, tenderness	Pulmonary embolus
Accentuated cardiac pulmonic sound, right ventricular heave	Pulmonary embolus, pulmonary arterial hypertension
Lymphadenopathy	Malignancy
Ascites	Cirrhosis
Friable, yellow nails	Yellow nail syndrome
Synovitis	Rheumatoid arthritis

Diagnostic Imaging

A chest radiograph should be performed as the first test in an evaluation of a possible pleural effusion. The radiographic findings are variable, but abnormalities may be seen with as little as 200 mL on the posterior-anterior chest radiograph or 50 mL on the lateral view (**Figure 11**).

Thoracic point-of-care ultrasonography is a helpful addition to chest radiography for identification of small effusions, particularly in patients who are semirecumbent, such as those who are critically ill (**Figure 12**). This imaging allows estimation of the quantity of the fluid and determination of whether it is free-flowing or loculated (i.e., with septations) (**Figure 13**). Ultrasonography is also associated with fewer complications when it is used to guide pleural procedures (such as thoracentesis).

The advantages of CT imaging with contrast include the ability to detect small amounts of pleural fluid; the assessment of coexisting intrathoracic abnormalities, such as pulmonary masses and malignant pleural disease; and identification of an empyema, as enhancement of the pleura around the fluid creates a lenticular-shaped opacity (**Figure 14**).

KEY POINTS

- A chest radiograph should be performed in the initial evaluation of possible pleural effusion.
- Thoracic ultrasound can characterize pleural effusions, quantify volume, and decrease complications when used to guide pleural procedures.

(Continued)

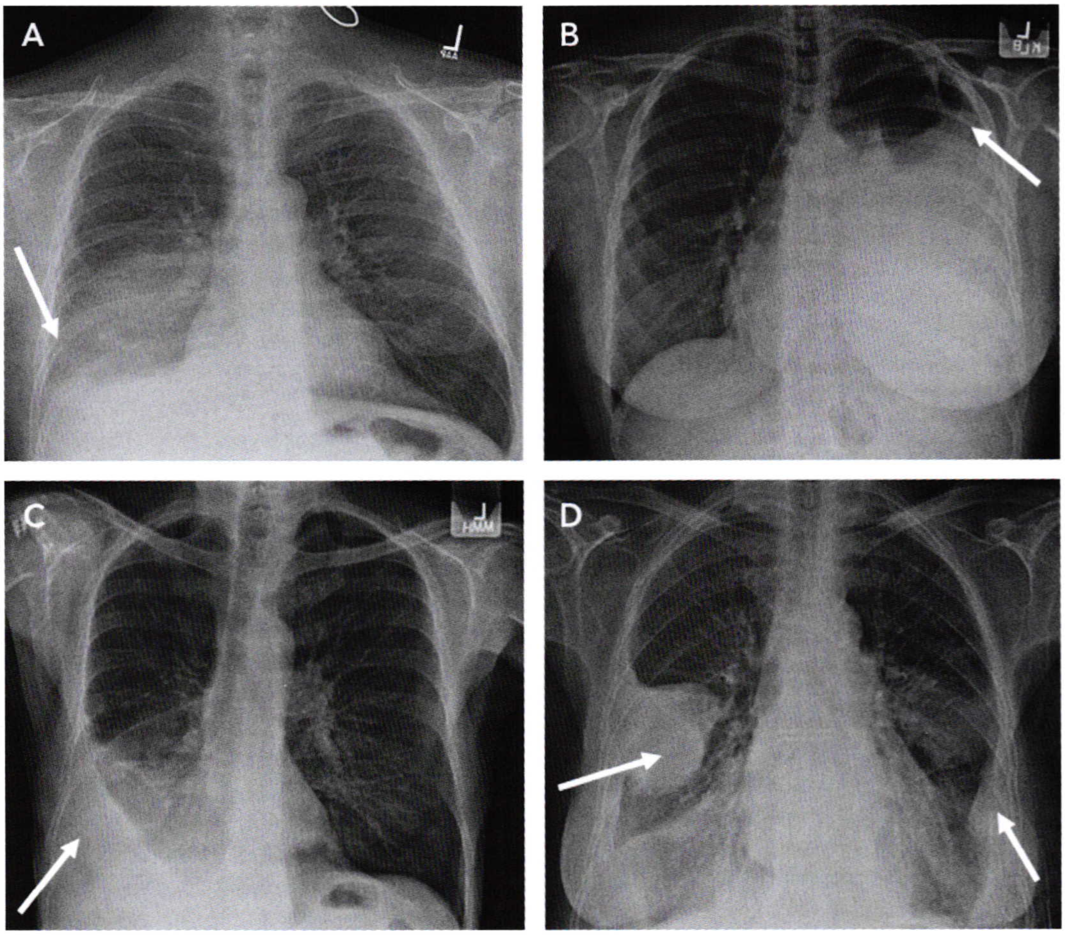


FIGURE 11. *A:* Moderate right pleural effusion that layers over the lower hemithorax. *B:* Large left pleural effusion with meniscus sign (a rim of fluid ascending the lateral chest wall). *C:* Loculated pleural effusion along the right lateral chest wall (presence of septations and separate compartments within the effusion). *D:* Bilateral multiloculated pleural effusions.

KEY POINTS ***(continued)***

HVC

- Thoracic ultrasound is more sensitive than chest radiography for the diagnosis of effusion in semirecumbent or supine patients, such as those who are critically ill, and in those with small effusions.

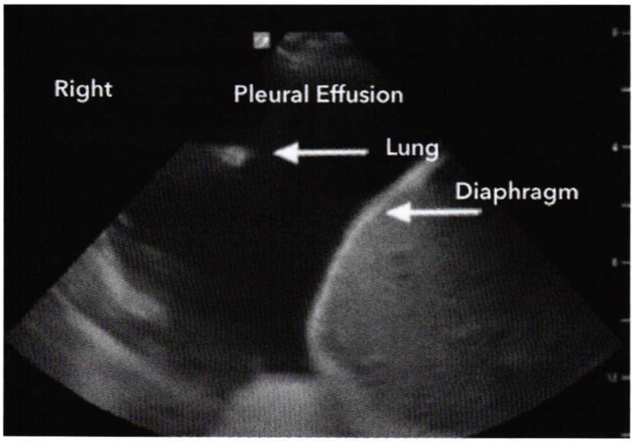


FIGURE 12. Moderate right-sided pleural effusion on ultrasound.

Indications for Thoracentesis

Once a pleural effusion is identified, the next diagnostic test to consider is thoracentesis.

Indications include pleural effusion of unknown cause and greater than 1 cm of fluid thickness on ultrasound or lateral decubitus radiograph. Thoracentesis should be performed with ultrasound guidance, as this allows for both a greater success rate and a reduced risk for solid organ puncture and iatrogenic pneumothorax.

Pleural Fluid Analysis

The first step in pleural fluid analysis is assessing the appearance of the pleural fluid (**Table 24**). The next step is to determine whether it is a transudate or exudate. Transudates are the result of an imbalance between hydrostatic and oncotic pressures, as occurs with heart failure and cirrhosis. Exudates are the result of inflammation causing increased capillary permeability, impaired drainage by lymphatics, or both. There are many causes of exudative effusions, but the most common are infection and malignancy. Differentiation is commonly made using Light's criteria (**Table 25**). These criteria are very sensitive for exudates—however, they are less specific, and

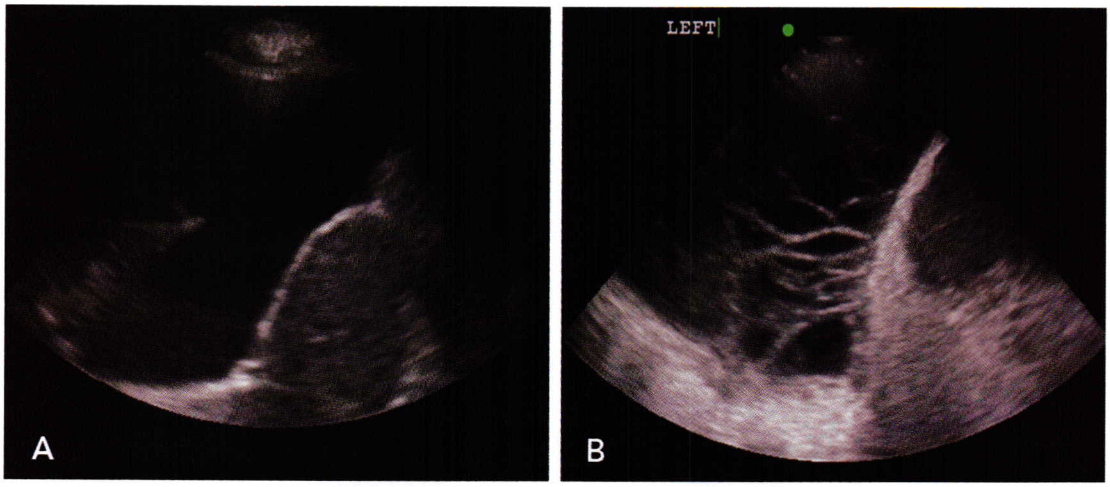


FIGURE 13. Comparison of a simple (*A*) and complicated (*B*) pleural effusion on thoracic ultrasound. A hypoechoic effusion (*A*) may be transudate or exudate. A multiseptated (loculated) effusion (*B*) is exudate.

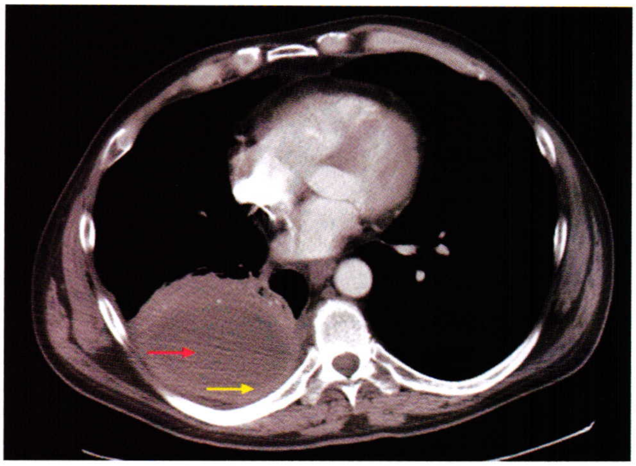


FIGURE 14. CT imaging reveals an empyema, as enhancement of the pleura around the fluid creates a lenticular-shaped opacity. The red arrow points to fluid pocket; the yellow arrow points to an area of pleural thickening.

approximately 25% of transudates are misclassified as exudates. In patients who have underlying heart failure and are receiving diuretics, a serum NT-pro B-type natriuretic peptide of greater than 1500 pg/mL is suggestive of a cardiac etiology for the effusion. Checking pleural fluid cholesterol is another accurate method for classifying an effusion as an exudate. Exudative and transudative effusions have a wide range of causes (**Table 26**).

In addition to characterizing a pleural effusion as a transudate or exudate, other tests are often performed on the basis of clinical suspicion. If infection is suspected, pH, glucose, cell count, Gram stain, and aerobic and anaerobic cultures should be performed. If malignancy is suspected, cytological analysis of fluid should be performed.

Cell Counts and Differential

Cell counts are useful for determining the cause of a pleural effusion—however, they are not disease-specific.

TABLE 24. Pleural Fluid Characteristics and Diagnostic Considerations

Appearance	Possible Causes	Additional Tests to Perform
Bloody	Malignancy, pulmonary embolus, trauma, pneumonia, benign asbestos pleural effusion	Hematocrit: if >50% of the serum, it is a hemothorax; consider aortic rupture, myocardial rupture, and injuries to hilar structures, lung parenchyma, and intercostal vessels
Milky	Chylothorax (most commonly seen after trauma or in patients with lymphoma) or cholesterol effusion (associated with tuberculosis and rheumatoid arthritis)	Triglyceride level
Yellow-green	Rheumatoid pleurisy	Serum rheumatoid factor Pleural fluid glucose <60 mg/dL (3.33 mmol/L)
Dark green	Bilothorax	Bilirubin
Dark brown/black	Long-standing hemothorax, fungal infection, malignancy	Hematocrit, cytology, fungal cultures
Purulent	Empyema	pH, glucose, cell count, gram stain, aerobic and anaerobic cultures

TABLE 25. Criteria for Exudative Pleural Effusion

Test	Sensitivity (%)	Specificity (%)
Combined Light's criteria (1 or more of the following 3):	97	85
Ratio of pleural fluid protein to serum protein level >0.5	90	90
Ratio of pleural fluid LDH level to serum LDH level >0.6	88	91
Pleural-fluid LDH level >2/3 the upper limit of normal for serum LDH	88-89	93-100
Pleural fluid cholesterol level >55 mg/dL	85-94	95-99
Ratio of pleural-fluid cholesterol to serum cholesterol >0.3	93	94

LDH = lactate dehydrogenase.

Data from Wilcox ME, Chong CA, Stanbrook MB, et al. Does this patient have an exudative pleural effusion? The Rational Clinical Examination systematic review. JAMA. 2014;311: 2422-2431. [PMID: 24938565] doi:10.1001/jama.2014.5552

TABLE 26. Causes of Transudates and Exudates

Transudates	Exudates
Very Common	
Heart failure	Parapneumonic
Cirrhosis	Malignancy
Less Common	
Nephrotic syndrome	Pulmonary embolism
Hypoalbuminemia	Tuberculosis
Unexpandable (trapped) lung	Autoimmune diseases (RA, SLE)
Peritoneal dialysis	Benign asbestos effusion
Atelectasis	Coronary artery bypass surgery
Urinothorax	Pancreatitis
Constrictive pericarditis	Myocardial infarction
Meigs syndrome (ovarian fibroma with ascites)	Yellow nail syndrome (lymphatic disorders)
Myxedema	Drugs (e.g., nitrofurantoin, dantrolene, methysergide, dasatinib, amiodarone, methotrexate, phenytoin, interleukin-2)
Pulmonary arterial hypertension	Sarcoidosis
	Abdominal disease (e.g., pancreatitis, esophageal perforation)

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

Neutrophil-predominant effusions are secondary to an acute process such as pneumonia (parapneumonic effusion) or pulmonary embolus. Lymphocyte predominance (more than 50%) is common in chronic effusions. The most common causes worldwide of lymphocyte-predominant effusions are tuberculosis and cancer. An effusion with greater than 10% eosinophils is most commonly caused by current or recent air or blood in the pleural space and is a nonspecific finding (**Table 27**).

Chemical Analysis

Pleural fluid acidosis (pH less than 7.3) is nonspecific and occurs in malignant effusions, complicated parapneumonic effusions, esophageal rupture, and inflammatory conditions such as rheumatoid and lupus pleuritis. A pH less than 7.2 in a parapneumonic effusion indicates that a complicated pleural effusion is present and tube thoracostomy drainage is needed. Glucose normally diffuses freely across the pleural membrane. A pleural glucose concentration of less than 60 mg/dL (3.33 mmol/L) narrows the differential significantly and suggests that the effusion is secondary to malignancy, empyema or complicated parapneumonic effusion, tuberculosis, esophageal rupture, or rheumatoid or lupus pleuritis.

Pleural fluid amylase concentration should be checked if there is concern that the effusion may be a result of pancreatitis or esophageal rupture. Pleural fluid amylase greater than the upper limit of normal for serum amylase or a pleural fluid to serum amylase ratio greater than 1.0 are indicative of pancreatitis or esophageal rupture.

TABLE 27. Pleural Cell Counts and Clinical Conditions

Cell Type	Cell Count	Clinical Conditions
Erythrocyte	5000-10,000/µL (5-10 × 10^9/L)	Hemothorax if pleural fluid hematocrit >50% peripheral hematocrit
Nucleated cells	>50,000/µL (50 × 10^9/L)	Complicated parapneumonic effusions and empyema
	>10,000/µL (10 × 10^9/L)	Simple parapneumonic effusion, acute pancreatitis, and lupus pleuritis
	<5000/µL (5 × 10^9/L)	Chronic exudates (TB pleuritis and malignancy)
Lymphocytes	>80%	TB, lymphoma, malignancy, RA pleuritis, sarcoidosis, late post-CABG effusions
Eosinophils	>10%	Air or blood in the pleural space; also parapneumonic effusions, drug-induced pleuritis, eosinophilic granulomatosis with polyangiitis, benign asbestos effusions, malignancy (lymphoma), pulmonary infarction, parasitic disease

CABG = coronary artery bypass graft; RA = rheumatoid arthritis; TB = tuberculosis.

Pleural fluid triglycerides elevated above 110 mg/dL (1.24 mmol/L) support the diagnosis of chylothorax. If the triglyceride level is between 50 and 110 mg/dL (0.56 and 1.24 mmol/L), the presence of chylomicrons should be checked. A true chylothorax results from a disruption of the thoracic duct and is usually the result of thoracic surgery or trauma. Other causes include malignancy (lymphoma), tuberculosis, and lymphatic malformations.

Tests for Tuberculous Effusions

The diagnosis of tuberculosis should be considered in a patient with a lymphocyte-predominant exudative effusion of unclear cause—however, confirming the diagnosis may be challenging. An acid-fast smear of pleural fluid has a sensitivity of less than 5%, and mycobacterial culture has a sensitivity of only 10% to 20% because of the low mycobacterial load. Adenosine deaminase is an enzyme present in lymphocytes that is elevated in most tuberculous pleural effusions (sensitivity, 90%). In countries with a low incidence of tuberculosis, testing for adenosine deaminase can be useful because a negative test helps to exclude tuberculosis. Pleural biopsy is useful for histology and is also the most likely source to yield a positive mycobacterial culture (greater than 70%).

Tests for Pleural Malignancy

Cytologic examination of pleural fluid has an average sensitivity of 60%. Sensitivity is slightly higher in adenocarcinoma (79%) and significantly lower in mesothelioma (6%), squamous cell carcinoma (14%), and lymphoma (40%). There is minimal benefit to obtaining and sending more than two fluid samples. If cytology is negative and malignancy is still suspected, pleural biopsy under direct visualization—known as thoracoscopy—may be the next step in evaluation. This procedure has a diagnostic sensitivity for malignant disease of greater than 90%. Closed pleural biopsy provides only a random sample of pleural tissue without visualization of pleural abnormalities. It is less sensitive than fluid cytology and has been replaced by thoracoscopy in the diagnostic evaluation of pleural malignancy.

Management

Parapneumonic Effusions and Empyema

A pleural effusion associated with a bacterial pneumonia is called a parapneumonic effusion. It can be uncomplicated (sterile and free flowing) or complicated (either infected or loculated). Uncomplicated effusions are typically small and resolve on their own with treatment of the pneumonia. Complicated parapneumonic effusions occur with significant inflammation or when bacteria invade the pleural space. An empyema is defined as a bacterial infection of the pleural space, which results in purulent fluid or a positive Gram stain. Pleural fluid cultures identify pathogens in only 60% of cases. If infection is suspected, culture bottles should be inoculated at the bedside to increase yield. Drainage is required if there is a positive Gram stain or culture or when the pH is less than 7.2. The bacteriology of pleural space infection differs depending on whether it is community-acquired or hospital-acquired. In the community, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Streptococcus anginosus* group are the organisms typically associated with pleural infection. Methicillin-resistant *S. aureus* and *Enterobacteriaceae* are more prevalent in nosocomial empyema. Anaerobic bacteria are cultured in greater than 20% of pleural space infections and may be a result of the common association with aspiration or the anaerobic environment of the pleural space. Polymicrobial infections are common, and empiric antibiotic regimens before obtaining culture results should include coverage for anaerobes.

Complicated parapneumonic effusions and empyema require drainage. Options for drainage include early surgical intervention via video-assisted thoracoscopic surgery and chest tube drainage with or without the combined use of intrapleural fibrinolytics (streptokinase, urokinase, tissue plasminogen activator) and a mucolytic agent (deoxyribonuclease, or DNase). There is controversy regarding which approach is best, and this question is under investigation. A multidisciplinary discussion should take place to help inform this decision.

Malignant Pleural Effusion

The diagnosis of a malignant pleural effusion signifies advanced disease and overall poor prognosis (usually 4-7 months from the time of diagnosis). In these cases, the goal of management is the relief of symptoms. Several therapeutic options exist, and treatment decisions should be based on symptoms, prognosis, degree of anticipated lung reexpansion, and patient performance status. Repeat therapeutic thoracentesis is appropriate for patients with poor prognosis (less than 3 months) and slow reaccumulation of fluid. Patients with rapid reaccumulation of fluid and dyspnea should be offered more definitive management. Indwelling pleural catheters with intermittent outpatient drainage provide significant symptom relief, and approximately 50% of patients achieve spontaneous pleurodesis after 6 to 8 weeks. Chemical pleurodesis refers to obliteration of the pleural space with a sclerosing agent (typically talc). Talc can be introduced through a thoracostomy tube (talc slurry) or during a thoracoscopy (talc poudrage). Talc pleurodesis is very effective, with a success rate of 60% to 90%, depending on the degree of lung reexpansion.

Nonmalignant Pleural Effusion

Recurrent benign pleural effusions portend a poor prognosis, as they are a marker of worsening of the underlying disease. Mortality rates of 50% in one year have been associated with effusions secondary to heart failure, 46% in those with kidney failure, and 25% in those with liver failure. As such, refractory benign effusions also deserve prompt attention. If diagnostic uncertainty persists, additional evaluation with imaging (chest CT with contrast) and possible thoracoscopy should be

TABLE 28. Risk Factors for Pneumothorax

Risk Factors for PSP
Smoking
Family history
Thoracic endometriosis
Tall stature
Risk Factors for SSP
COPD
Interstitial lung disease
Tuberculosis
Cystic fibrosis
Malignancy
Necrotizing pneumonia
Marfan syndrome

PSP = primary spontaneous pneumothorax; SSP = secondary spontaneous pneumothorax.

considered. Options for management include tunneled pleural catheters, pleurodesis, or both after careful discussion with a multidisciplinary team.

Pneumothorax

Evaluation

Pneumothorax is defined as air in the pleural space, which can occur spontaneously or as a result of trauma or a procedural complication. A primary spontaneous pneumothorax (PSP) occurs in someone without known underlying lung disease. A secondary spontaneous pneumothorax (SSP) occurs in someone with a known underlying lung disease such as COPD. Risk for recurrence for PSP is 23% to 50% over the course of 1 to 5 years and greater than 50% over the course of 1 to 3 years in those with SSP. Risk factors for pneumothorax are listed in **Table 28**.

Symptoms include sudden onset of dyspnea and sharp pleuritic chest pain. The symptoms are typically more severe with SSP because patients have less respiratory reserve. Physical examination findings can be subtle but usually reveal reduced lung expansion, hyperresonance to percussion, and diminished breath sounds on the side of the pneumothorax. Tension pneumothorax should be suspected in patients presenting with significant cardiorespiratory distress (worsening dyspnea, hypotension, absent breath sounds on one side, tracheal deviation, and distended neck veins).

A chest radiograph is an appropriate initial test and can confirm the diagnosis and determine the size of the pneumothorax. If the lung margin is greater than 2 cm away from the chest wall at the level of the hilum, it is considered a large pneumothorax (**Figure 15**). CT is the most sensitive imaging modality for small pneumothoraces and is particularly useful in patients with bullous emphysema. Ultrasound can also be helpful in the diagnosis of pneumothorax, with the presence of lung sliding indicating no pneumothorax at that specific location and the presence of a lung point confirming the edge of a pneumothorax.

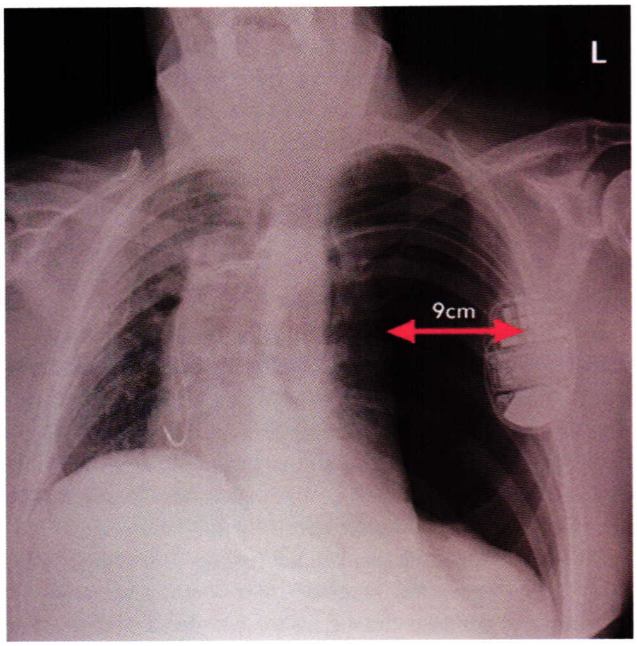


FIGURE 15. Large left-sided pneumothorax (>2 cm at the hilum).

Management

Management of pneumothorax is driven by clinical symptoms. A tension pneumothorax (large and hemodynamically significant) should be managed by emergent needle thoracostomy followed by thoracostomy tube placement and hospitalization. Observation alone has been shown to be safe for small pneumothoraces in patients with minimal symptoms (**Table 29**).

TABLE 29. Management of Pneumothorax

Size[a] and Clinical Symptoms	Management
<2 cm on chest radiograph, minimal symptoms	Needle aspiration or admit to hospital for observation and supplemental oxygen (PSP may be managed as an outpatient if good access to medical care)
>2 cm on chest radiograph, breathlessness, and chest pain	Insertion of a small-bore (<14 Fr) thoracostomy tube with connection to a high-volume low-pressure suction system
Cardiovascular compromise (hypotension, increasing breathlessness) regardless of size	Emergent needle decompression followed by thoracostomy tube insertion Note: If persistent air leak (>48 hours), refer to an interventional pulmonologist or thoracic surgeon

PSP = primary spontaneous pneumothorax.

[a] Measured between lung and chest wall at the level of the hilum.

Recurrence prevention is recommended after the second episode of pneumothorax on the ipsilateral side in PSP and after the first occurrence in SSP. Patients should be encouraged to stop smoking; the lifetime incidence rates for PSP are much higher in men who are lifelong heavy smokers than in men who have never smoked (12% vs 0.1%). Intervention to prevent recurrence includes both chemical and mechanical pleurodesis. Air travel should be avoided until complete resolution of the pneumothorax, and scuba diving is not recommended unless definitive therapy such as surgical pleurectomy has been applied.

Pulmonary Vascular Disease

Pulmonary Hypertension

Pulmonary hypertension (PH) has been defined as a resting mean pulmonary artery pressure (mPAP) of 25 mm Hg or greater, measured by right heart catheterization. A normal resting mPAP is around 14 mm Hg and is rarely above 20 mm Hg. In 2018, based on growing evidence that patients with mPAP above 20 mm Hg are at increased risk for early mortality, the Sixth World Symposium on Pulmonary Hypertension revised the definition of PH to include all patients with a resting mPAP of 20 mm Hg or greater.

PH can occur for a variety of reasons. The current classification system separates PH into five groups on the basis of similarities in mechanisms, hemodynamics, clinical presentation, and approach to treatment (**Table 30**).

Evaluation of Suspected Pulmonary Hypertension

Symptoms of PH are nonspecific; thus, the average time from symptom onset to diagnosis can exceed 2 years. Symptoms include exertional dyspnea or lightheadedness, lower extremity edema, chest pain, palpitations, and in some cases syncope. As pulmonary vascular remodeling in PH progresses, pulmonary artery (PA) pressures rise. Right ventricular (RV) remodeling and compensation initially occur to maintain normal cardiac output. In the face of disease progression, the compensatory mechanisms of the RV eventually fail. At this point, patients begin to experience the classic symptoms of RV failure associated with PH.

TABLE 30. Classification of Pulmonary Hypertension

1	Pulmonary arterial hypertension (includes idiopathic and heritable disease, disease associated with use of drugs or toxins, connective tissue diseases, HIV infection, congenital heart disease, schistosomiasis, and portal hypertension; also includes vasoresponsive PAH and PAH attributable to pulmonary venoocclusive disease or pulmonary capillary hemangiomatosis)
2	Pulmonary hypertension due to left-sided heart disease
3	Pulmonary hypertension due to lung diseases or hypoxia
4	Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
5	Pulmonary hypertension with unclear or multifactorial causes

PAH = pulmonary arterial hypertension.

Information from Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53. [PMID: 30545968] doi:10.1183/13993003.01913-2018

Findings on physical examination frequently include an accentuated or persistently split second heart sound. A tricuspid regurgitant murmur may be detected, and jugular venous distention, an RV heave, hepatomegaly, ascites, and peripheral edema occur in the face of progressive RV failure. Pulmonary findings reflect underlying lung disease when present.

If PH is suspected, transthoracic echocardiography should be pursued (**Figure 16**). Echocardiography provides an estimation of PA systolic pressure and assessment of both right and left heart size and function (**Figure 17**). If the echocardiogram suggests PH, the patient should be referred for further evaluation, including right heart catheterization. Echocardiography should not be used to confirm a PH diagnosis because the PA pressure measurement is often inaccurate when measured using echocardiography.

Right heart catheterization is essential to confirm a diagnosis of PH, as it provides accurate hemodynamic data and helps distinguish the primary cause of elevated PA pressure.

An evaluation for suspected PH should also include pulmonary function tests, high-resolution CT (if interstitial lung disease is a consideration), and tests for sleep-related breathing disorders; to detect the etiology of some forms of PH, serologic tests for underlying connective tissue disease, hepatitis, and HIV are advised. All patients with suspected PH should receive a ventilation/perfusion (V/Q) scan to evaluate for chronic thromboembolic PH (CTEPH). V/Q offers improved sensitivity over CT angiography (CTA) when evaluating for CTEPH. Assessment of functional status with the 6-minute walk test provides prognostic information and a baseline for assessment of therapeutic response.

KEY POINTS

- If pulmonary hypertension is suspected, transthoracic echocardiography should be performed to estimate pulmonary artery systolic pressure and assessment of right and left heart size and function.
- Right heart catheterization is essential to confirm a diagnosis of pulmonary hypertension, as it provides accurate hemodynamic data and helps distinguish the primary cause of elevated pulmonary artery pressure. **HVC**

Pulmonary Arterial Hypertension (Group 1)

Pulmonary arterial hypertension (PAH) is defined by elevated pulmonary vascular resistance in the small pulmonary

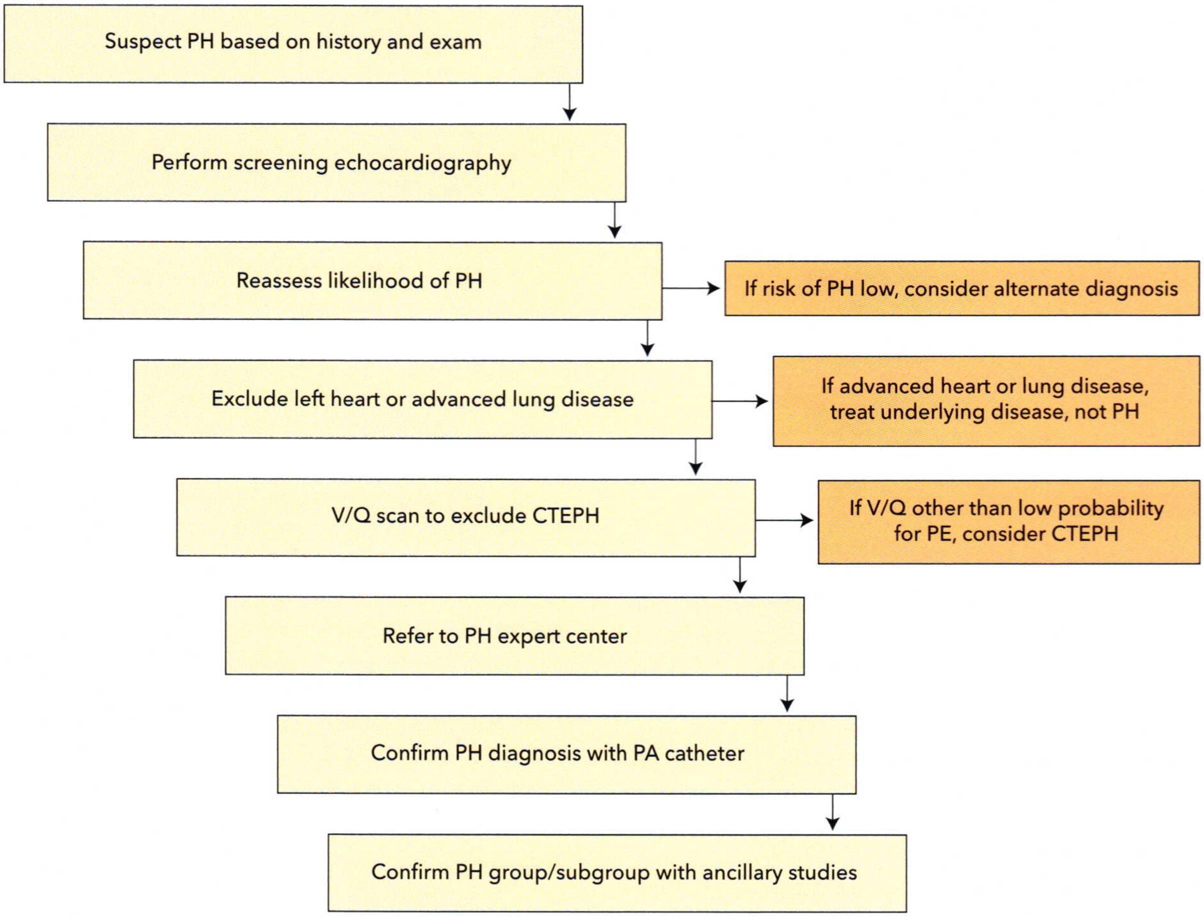

Suspect PH based on history and exam
Perform screening echocardiography
Reassess likelihood of PH
If risk of PH low, consider alternate diagnosis
Exclude left heart or advanced lung disease
If advanced heart or lung disease, treat underlying disease, not PH
V/Q scan to exclude CTEPH
If V/Q other than low probability for PE, consider CTEPH
Refer to PH expert center
Confirm PH diagnosis with PA catheter
Confirm PH group/subgroup with ancillary studies

FIGURE 16. Algorithm for the evaluation of pulmonary hypertension. CTEPH = chronic thromboembolic pulmonary hypertension; PA = pulmonary artery; PE = pulmonary embolism; PH = pulmonary hypertension; V/Q = ventilation/perfusion.

Adapted from Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J. 2019;53. [PMID: 30545972] doi:10.1183/13993003.01904-2018. Modified and reproduced with the permission of the © ERS 2021.

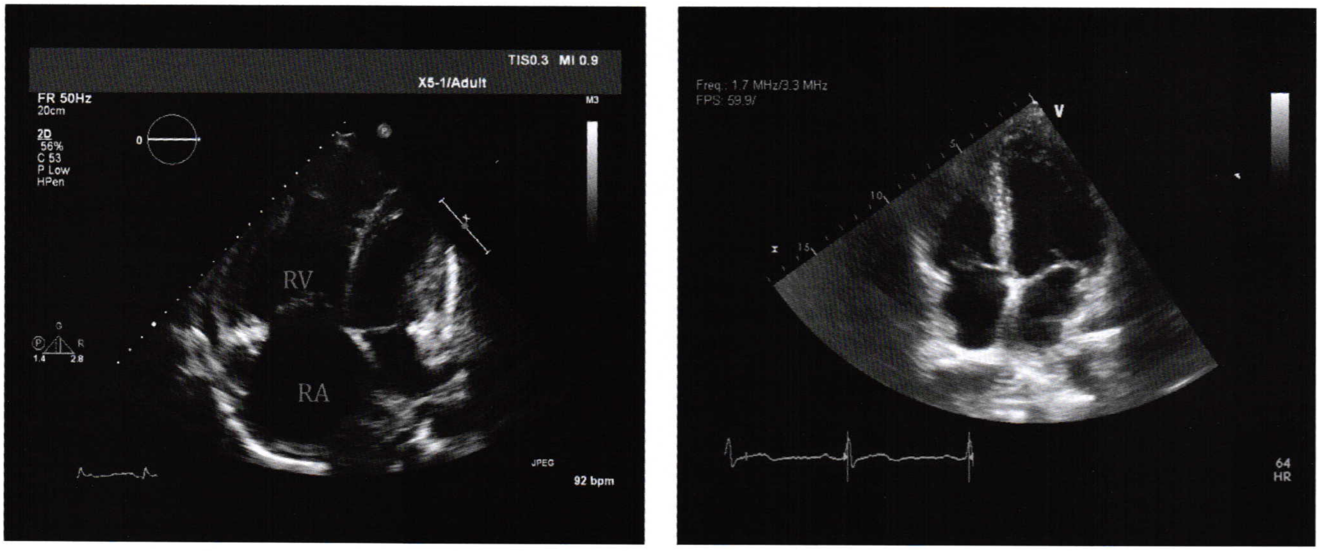

TIS0.3 MI 0.9
X5-1/Adult
FR 50Hz
20cm
2D
56%
C 53
P Low
HPen
M3
RV
RA
JPEG
92 bpm
Freq.: 1.7 MHz/3.3 MHz
FPS: 59.9/
V
64
HR

FIGURE 17. Apical four-chamber views of echocardiograms from a patient with idiopathic pulmonary arterial hypertension (left) and a healthy person (right). As seen here, dilation of the right ventricle and right atrium is a common finding in patients with pulmonary arterial hypertension.

Reproduced with permission, from Poch D, Mandel J. Pulmonary hypertension. Ann Intern Med. 2021;174:ITC49-ITC64. [PMID: 33844574] doi:10.7326/AITC202104200. Copyright 2021, American College of Physicians.

arterioles. Imbalances in nitric oxide, prostacyclin, and endothelin affect vascular tone and endothelial and smooth muscle cellular growth and lead to vascular narrowing. Accordingly, these pathways are the primary targets for available therapy.

There are several subclassifications of group 1 PAH based on etiology of disease (see Table 30). Idiopathic PAH (previously referred to as primary PH) is typically seen in middle-aged adults, particularly women. Heritable forms account for up to 10% of cases, with the majority attributable to autosomal-dominant mutations in bone morphogenetic protein receptor type 2 (*BMPR2*). PAH can also occur in association with connective tissue diseases, portal hypertension, congenital heart disease, HIV infection, drug use, and toxin exposure.

Approximately 10% of patients with systemic sclerosis develop PAH. In these patients, disease is often refractory to treatment and outcomes are worse than in PAH from other causes. Patients with limited cutaneous systemic sclerosis may be at the highest risk. PAH can rarely be seen in rheumatoid arthritis and systemic lupus erythematosus.

Portopulmonary hypertension affects some patients who have chronic liver disease (see MKSAP 19 Gastroenterology and Hepatology). The mechanism remains unclear, but it may be related to the diseased liver's inability to metabolize vasoactive substances.

PAH in patients with HIV infection is not common, but HIV-infected patients have a disproportionately higher risk of developing PAH compared with patients without HIV infection. Both viral and host factors have been implicated, and disease can occur in the absence of AIDS-related complications. The drugs most strongly associated with PAH are listed in **Table 31**.

TABLE 31. Drugs and Toxins Associated With Pulmonary Arterial Hypertension

Rapeseed oil
Aminorex/dexfenfluramine/benfluorex
Hepatitis C antiviral therapies
Interferon α and β
Dasatinib and bosutinib
Methamphetamines and other amphetamines
Cocaine
Phenylpropanolamine
L-tryptophan
St John's wort
Indirubin
Leflunomide
Alkylating agents

Information from Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53. [PMID: 30545968] doi:10.1183/13993003.01913-2018

KEY POINT

- Pulmonary arterial hypertension can occur in association with connective tissue diseases, portal hypertension, congenital heart disease, HIV infection, drug use, and toxin exposure.

Diagnosis

The diagnosis of PAH requires an elevated mPAP attributable to high pulmonary vascular resistance. Cardiac output and pulmonary capillary wedge pressure should be normal or low, and left heart or lung disease should be excluded as a potential cause. Lung biopsy poses a significant risk for patients with PAH and is not indicated in the diagnostic evaluation. Laboratory studies can identify potential causes for PAH and should include HIV serologies, liver chemistries, thyroid function tests, and autoantibody titers including antinuclear antibody. Pulmonary function testing that is normal, with the exception of a marked decrease in D_{LCO}, supports a diagnosis of PAH. Current guidelines recommend genetic screening for all patients with idiopathic PAH or PAH associated with anorexigenic drugs (intended to reduce the appetite), as well as for patients with a family history of PAH.

KEY POINT

- The diagnosis of pulmonary arterial hypertension requires an elevated mean pulmonary artery pressure attributable to high pulmonary vascular resistance.

Management

Therapy for PAH is directed at reducing vasoconstriction and interrupting the pathways mediating cellular proliferation. Initial therapy should be determined on the basis of disease severity (**Table 32**). In most patients, a combination of PH-specific therapies targeting separate pathways within the pulmonary circulation is associated with superior outcomes compared with single-agent therapy. In a small proportion of patients, high-dose calcium channel blockers are effective. Calcium channel blockers should be reserved for "vasoreactive" patients who demonstrate marked improvement in mPAP with the administration of nitric oxide, epoprostenol, or adenosine during right heart catheterization. Although survival among vasoreactive patients is superior to that among other patients with PAH, close follow-up of these patients is required, as many become nonvasoreactive within a few years of diagnosis and subsequently require conventional PAH therapy. The absence of vasoreactivity during right heart catheterization does not suggest that a patient will not benefit from appropriate PAH therapy.

Additional treatments include diuretic therapy and a low-sodium diet to combat volume overload. Women of reproductive age who have PAH should be counseled on the risks of pregnancy and advised against it. In patients with atrial fibrillation, attempts to restore normal sinus rhythm should be pursued, as

TABLE 32. Pharmacologic Therapy for Pulmonary Arterial Hypertension

Class	Comments
Calcium channel blockers	Only for patients with acute vasodilator response at catheterization; acute response does not ensure chronic response; adverse effects such as hypotension can occur.
Prostacyclin analogues (epoprostenol, treprostinil, iloprost)	Parenteral prostacyclin analogues such as epoprostenol, administered by a continuous central venous or subcutaneous infusion, are first-line therapy for severe disease and for those in whom disease progresses despite oral therapy; inhaled iloprost and treprostinil require frequent administration; oral treprostinil is most effective at higher doses (≥9 mg/day); prostanoids supplement endogenous levels of prostacyclin (PGI_2), a vasodilator with antismooth muscle proliferative properties.
Prostacyclin receptor agonist (selexipag)	Works as an oral prostacyclin agonist. Current guidelines do not make recommendations for or against the use of selexipag for mild to moderate disease.[a]
Endothelin-1 receptor antagonists (bosentan, ambrisentan, macitentan)	Reasonable initial oral therapies for mild to moderate disease.[b] Blocks action of endogenous vasoconstrictor and smooth muscle mitogen endothelin; class-wide risk for liver injury and teratogenicity. Bosentan caries significant risk for liver injury and requires serial liver chemistry testing.[c] Continuous pregnancy testing for reproductive-aged women is required.
Phosphodiesterase-5 inhibitors (sildenafil, tadalafil)	Reasonable initial oral therapies for mild to moderate disease.[b] Prolongs effect of intrinsic vasodilator cyclic GMP by inhibiting hydrolysis by phosphodiesterase-5.
Soluble cyclic GMP stimulators (riociguat)	Reasonable initial oral therapy for mild to moderate disease. Works by directly stimulating guanylate cyclase receptor, independent of endogenous NO, to promote pulmonary artery vasodilation.

GMP = guanosine monophosphate; NO = nitric oxide.

[a] The 2018 CHEST Guidelines for the treatment of pulmonary hypertension in adults made recommendations based largely on 6-minute walk test improvements in patients on various therapies. Selexipag improved other patient outcomes in a large, double-blind placebo controlled randomized clinical trial (GRIPHON). The guideline committee acknowledged that selexipag improved outcomes in other areas than the 6-minute walk test but did not recommend for or against its use given only modest improvement of 12 m in the treatment group compared with placebo.

[b] Combination therapy with ambrisentan and tadalafil is the recommended first-line therapy in if the patient is willing and able to tolerate it.

[c] Although not required for ambrisentan, some experts suggest that it is prudent to perform liver chemistry tests at the outset of treatment for pulmonary arterial hypertension and at periodic intervals thereafter at the discretion of the managing physician.

persistent atrial fibrillation in patients with PAH is associated with increased mortality. Supervised exercise training improves functional capacity and use of palliative care resources by patients with PAH can improve patient function and quality of life. In patients for whom drug therapy is unsuccessful, referral for lung or heart-lung transplantation should be considered.

Chronic Thromboembolic Pulmonary Hypertension (Group 4)

CTEPH is composed of organized, chronic thrombi within the pulmonary arterial system. Patients with CTEPH demonstrate both mechanical obstruction of pulmonary arteries as well as features of disordered pulmonary angiogenesis, fibrinolysis, and vascular remodeling. These changes manifest in increased pulmonary vascular resistance and elevated mPAP. Untreated, CTEPH can lead to right heart failure and death. Although it is likely that fewer than 5% of patients who experience an acute pulmonary embolism (PE) develop CTEPH, more than 1 in 5 patients diagnosed with CTEPH do not have a documented history of PE. For further discussion of acute PE, see MKSAP 19 Hematology.

Diagnosis

Because a history of prior PE is not always evident in patients diagnosed with CTEPH, it remains an underrecognized cause of PH and requires a high index of suspicion. In patients diagnosed with PH, evaluation for CTEPH is warranted, even when a history of acute PE is absent. Current guidelines recommend a V/Q scan to rule out CTEPH in all patients being evaluated for PH despite rapidly improving CT scanner technology and imaging techniques. A normal V/Q is sufficient to exclude CTEPH, as its sensitivity for detecting chronic thrombus approaches 100%.

There are few data to suggest that treatment of acute PE, including thrombolytic therapy or mechanical thrombectomy, reduces a patient's risk for subsequent CTEPH. Although guidelines do not recommend follow-up CTEPH screening for all patients who present with acute PE, the diagnosis should be considered in any patient who remains symptomatic or develops symptoms consistent with PH after 3 months of anticoagulation. In addition, current guidelines recommend that patients with CTEPH undergo screening for thrombophilia. This includes testing for anticardiolipin antibody, antiphospholipid antibody, and lupus anticoagulant.

When V/Q scan suggests chronic thrombus, additional imaging to characterize vascular anatomy and to evaluate the extent of CTEPH is indicated. Digital subtraction angiography has long been the gold standard for this. But recent advances in pulmonary CTA have led many experts to prefer CTA because it is less invasive than digital subtraction angiography and in many cases offers excellent resolution and identification of pertinent vascular anomalies such as webs, intimal irregularities, and luminal narrowing. CTA may be less sensitive for more distal lesions.

KEY POINT

HVC
- Patients with pulmonary hypertension should be evaluated for chronic thromboembolic pulmonary hypertension with a ventilation/perfusion scan.

Management

Anticoagulation and consideration of thromboendarterectomy are indicated for CTEPH. Lifelong anticoagulant therapy is indicated in all patients to help prevent further thromboembolism. The only potentially curative therapy for CTEPH is pulmonary thromboendarterectomy. Because the disease is usually progressive, surgical evaluation at an experienced center is warranted in all patients with CTEPH regardless of disease severity. About half of patients with CTEPH will be eligible for surgery. Pulmonary thromboendarterectomy can result in the normalization of pulmonary hemodynamics in about one-third of patients who undergo surgery. In patients who are deemed inoperable by one expert center, referral for a second opinion is recommended by guidelines. In inoperable patients and those who have persistent PH after thromboendarterectomy, balloon pulmonary angioplasty or medical therapy should be considered. Riociguat, a pulmonary vasodilator that acts on the nitric oxide pathway, is currently the only approved PH therapy available for CTEPH treatment. Balloon pulmonary angioplasty has recently emerged as an alternative option in nonoperable patients and those with persistent PH after thromboendarterectomy. Study results have been promising as patients show improved overall outcomes including PA hemodynamics, RV function, and symptoms. Balloon pulmonary angioplasty is not recommended as an alternative to thromboendarterectomy, given insufficient data to suggest equivalent outcomes between the two procedures.

Other Types of Pulmonary Hypertension (Groups 2, 3, and 5)

The majority of PH is attributable to left-sided heart disease (group 2) and hypoxic respiratory disorders (group 3). Left-sided heart disease (heart failure with reduced or preserved ejection fraction and mitral or aortic valvular disease) results in elevations in left atrial and pulmonary venous pressures. Chronic hypoxia is the most likely nidus for pulmonary vascular remodeling in PH related to advanced respiratory disorders such as COPD, interstitial lung disease, and sleep hypoventilation syndromes. In patients with COPD and emphysema, obliteration of the vascular bed also contributes to elevated pulmonary vascular resistance; management focuses on ensuring sufficient oxygen requirements. In patients with left heart disease or advanced lung disease, the presence of PH increases the risk for death; management typically involves cautious diuresis and arrhythmia treatment.

A small minority of PH cases are caused by diseases that do not share any particular clinical or pathologic similarities or in which the mechanisms of pulmonary vascular disease are poorly understood (group 5). Diseases such as sarcoidosis, multiple myeloma, and other myeloproliferative neoplasms, complex congenital heart disease, and a variety of other disorders are included in this classification.

KEY POINT

- The majority of pulmonary hypertension is attributable to left-sided heart disease and hypoxic respiratory disorders.

Diagnosis

Not all patients with PH will fall exclusively in one category. For example, patients with connective tissue disease-related PAH can have concomitant heart disease that contributes to PH. Group 2 PH is often determined on the basis of abnormalities identified on echocardiography and a hemodynamic profile consistent with elevated left atrial pressure (measured by PA wedge pressure on right heart catheterization) greater than 15 mm Hg. The hemodynamic profile of patients with group 3 PH mirrors that of patients with PAH and CTEPH. Patient history of advanced lung disease in addition to abnormal chest imaging (radiograph or CT scan) or pulmonary function testing is essential to identifying group 3 disease. Significant abnormalities on imaging or pulmonary function testing should prompt further attention toward treatment of the underlying lung disease, not the PH. Chronic nocturnal hypoxia associated with sleep-disordered breathing is also associated with PH. Studies show that the prevalence of nocturnal hypoxia in patients with PH is as high as 89%. Common screening studies such as the Epworth sleepiness scale do not offer reliable sensitivity to exclude sleep-disordered breathing in this population. Current guidelines suggest considering an evaluation for sleep-disordered breathing or nocturnal hypoxia with polysomnography or home sleep study in patients with PH.

Lung Tumors

Pulmonary Nodule Evaluation

Pulmonary nodules appear on radiography as small radiographic opacities (less than 3 cm in size) surrounded by normal lung parenchyma. These nodules are asymptomatic and found either incidentally or on screening. In contrast, a focal pulmonary opacity larger than 3 cm is considered a lung mass and is presumed malignant until proved otherwise.

The finding of a pulmonary nodule is increasingly common because of the frequency of CT scans performed for other reasons, as well as lung cancer screening programs. Management of these lesions can be complicated and often requires subspecialty referral. Principles of pulmonary nodule evaluation include reviewing imaging history, estimating the probability of malignancy, and discussing management preferences with the patient. Guidelines recommend management based on nodule size and characteristics. When more than one nodule is present, follow-up is dictated by the size and characteristics of the largest lesion. Shared decision-making is an integral part of the evaluation and management of pulmonary nodules.

KEY POINTS

- Principles of pulmonary nodule evaluation include the review of imaging history, estimating the probability of malignancy, and discussing management preferences with the patient.
- A focal pulmonary opacity larger than 3 cm is presumed malignant until proved otherwise.

Solid Indeterminate Nodule Larger Than 8 mm

The first step in evaluating a solid nodule that is larger than 8 mm in size is to estimate the probability of malignancy. Criteria included in the calculation include age, smoking history, nodule size, location within the lung, and presence of spiculated or lobular border. (Lung cancer risk calculators can be accessed at https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/.) Solid nodules with moderate probability of malignancy should be characterized further with a PET scan. If the PET scan is negative for metabolic activity, continued surveillance is warranted (**Table 33**). A nodule with moderate or intense uptake is suggestive of malignancy and requires referral for further evaluation.

If the probability of malignancy is initially high, the next step is staging with a PET scan followed by definitive management with surgical resection or chemotherapy and radiation.

KEY POINT

- The first step in evaluating a solid pulmonary nodule larger than 8 mm in size is to estimate the probability of malignancy.

Solid Indeterminate Nodule of 8 mm or Smaller

Solid indeterminate nodules of 8 mm or smaller are usually detected incidentally. The first step, as with larger nodules, is an estimation of the likelihood of malignancy (https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/). Nodules of 8 mm or smaller have a lower probability of being malignant, are difficult to biopsy, and are not reliably characterized by PET scan. As a result, these small nodules are usually followed by serial CT scans. The frequency and duration of follow-up is based on the recommendations of the Fleischner Society and endorsed by other professional societies (see Table 33).

TABLE 33. Fleischner Society Recommendations for Single Pulmonary Nodule Follow-Up

Risk Factors for Lung Cancer?	Size	Recommended Follow-Up
No (Low-risk patient)	<6 mm	No follow-up
	6-8 mm	CT at 6-12 months, then consider CT at 18-24 months
	>8 mm	Consider CT at 3 months, PET/CT, or tissue sampling
Yes (High-risk patient)	<6 mm	Optional CT at 12 months
	6-8 mm	CT at 6-12 months, then CT at 18-24 months
	>8 mm	Consider CT at 3 months, PET/CT, or tissue sampling

Adapted with permission, from MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659. Copyright 2017, RSNA.

Subsolid Nodule

A subsolid nodule is a focal rounded opacity that is either pure ground glass in appearance (focal density with underlying lung architecture still preserved) or has a solid component (part solid) but is still more than 50% ground glass (**Figure 18**). These nodules often represent premalignant disease, such as adenocarcinoma in situ, and can be very slow growing.

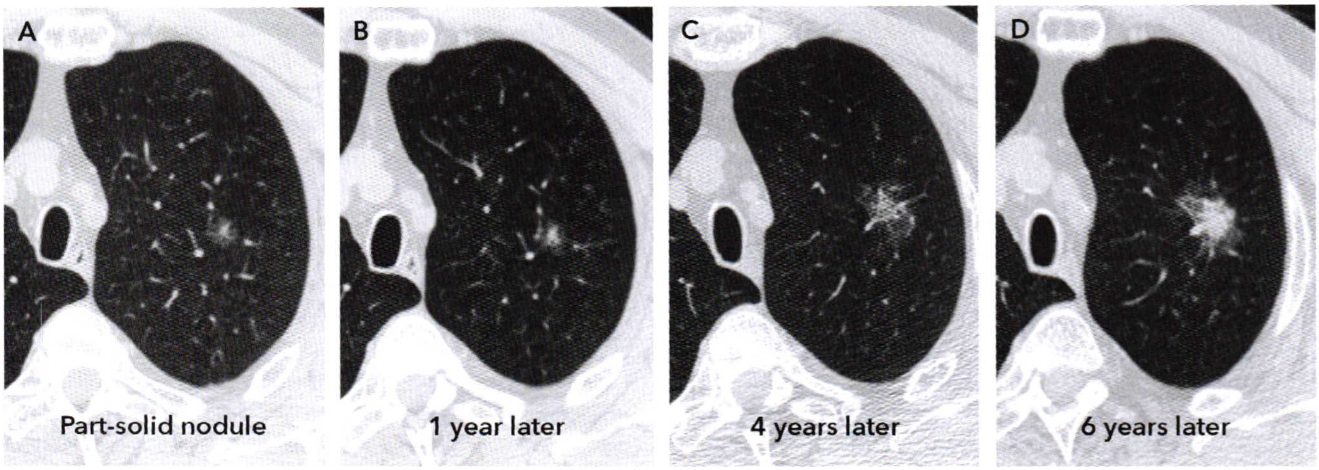


FIGURE 18. Radiographs show the evolution of a part-solid nodule from adenocarcinoma in situ to invasive adenocarcinoma: part-solid, part-ground-glass nodule in the left upper lobe (*A*); growth in the solid component of the nodule 1 year after initial imaging (*B*); an increase in size in the ground-glass component 4 years after initial imaging (*C*); and further increase in the solid component of the nodule 6 years after initial imaging (*D*). This growth rate is characteristic of a part-solid, part-ground-glass nodule and demonstrates why patients with this finding must be followed for at least 5 years.

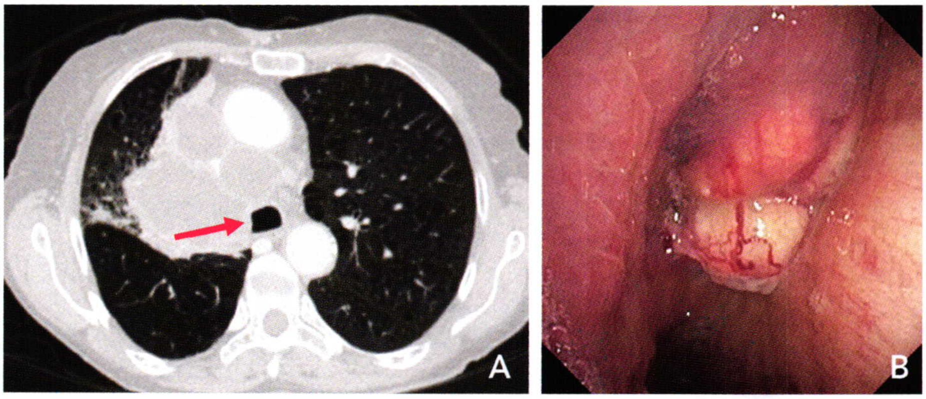


FIGURE 19. Metastatic squamous cell carcinoma can be seen as an 8-cm right hilar mass with invasion into the trachea on CT scan (*A*) and as tumor invasion into the distal trachea and occlusion of the right main stem on bronchoscopy (*B*).

Observed doubling times can range between 400 and 800 days. This has implications for both the frequency and the duration of follow-up. Subsolid nodules are not reliably characterized by PET scans, and nonsurgical biopsies also have limited sensitivity. Development of a solid component in a pure groundglass nodule or enlargement of the solid component suggests malignancy (see Figure 18). Recommendations for nonsolid and part-solid nodule follow-up are in **Table 34**.

Lung Cancer

Lung cancer is the leading cause of cancer death worldwide. In the United States, it is estimated that 230,000 new cases will be diagnosed and more than 135,000 deaths will occur annually. The overall 5-year survival rate remains low, at 17.7%. However, much progress has been made recently regarding screening, diagnosis, and treatment.

KEY POINT

- Lung cancer is the leading cause of cancer death worldwide.

Lung Cancer Types

There are two major classes of lung cancer: non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Approximately 80% of lung cancer cases are NSCLC, which is divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most common NSCLC and accounts for almost all lung cancer diagnoses in nonsmokers. The most frequent location of adenocarcinoma is in the peripheral aspects of the lung parenchyma as a solitary nodule or mass. Squamous cell carcinoma is the second most common subtype of NSCLC. It correlates highly with smoking history and usually originates in the central airways (trachea, main stem bronchi, lobar and segmental bronchi) (**Figure 19**). Individuals with squamous cell carcinoma often have symptoms of cough and hemoptysis caused by central airway involvement. Radiographically, squamous cell carcinoma may present with postobstructive pneumonia or lobar collapse. Large cell carcinoma is an undifferentiated carcinoma and characteristically presents as a peripheral mass with prominent necrosis (**Figure 20**).

In the past decade, the development of targeted therapy for specific gene mutations has allowed for the individualization of therapy and improved survival. Testing for epidermal growth factor receptor (*EGFR*) mutation, anaplastic

TABLE 34. Fleischner Society Recommendations for Solitary Subsolid Lung Nodule Follow-Up

Imaging Findings	Size	Recommended Follow-Up
Pure ground glass	<6 mm	No follow-up
	≥6 mm	CT at 6-12 months to confirm persistence, then CT every 2 years until 5 years
Part solid nodule	<6 mm	No follow-up
	≥6 mm	CT at 3-6 months to confirm persistence; if unchanged and solid component remains <6 mm, annual CT should be performed for 5 years

Adapted with permission, from MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659. Copyright 2017, RSNA.

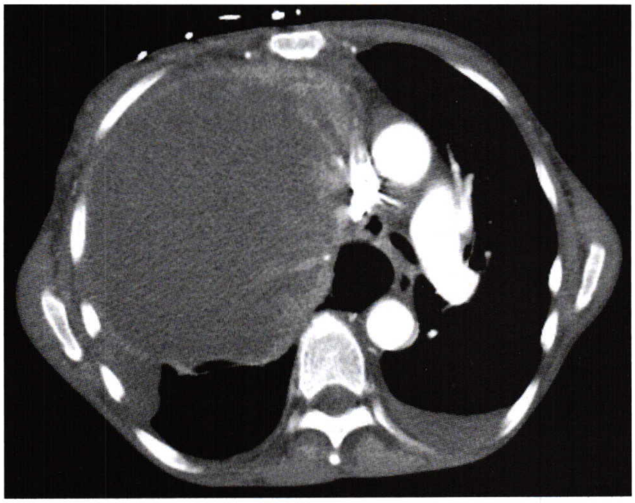


FIGURE 20. Large cell carcinoma with predominant necrosis can be seen on CT scan as a large necrotic tumor that has completely replaced the right upper and middle lobes, with deviation of the central airway structures to the left. Necrosis is noted by the mixed attenuation of the mass, as noted on CT.

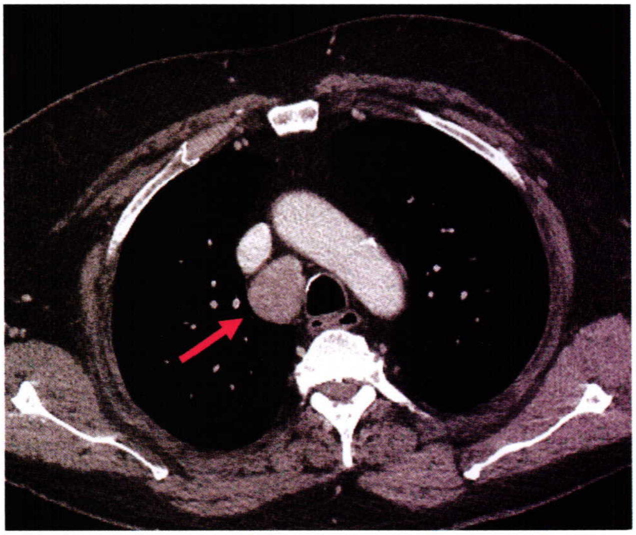


FIGURE 21. Small cell lung cancer can be seen on chest CT with a right paratracheal mass (*arrow*). This patient initially presented with encephalitis (paraneoplastic syndrome).

lymphoma kinase receptor tyrosine kinase (*ALK*) translocation, and ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*) translocation is recommended in advanced-stage adenocarcinoma or mixed cancers. The role for immunotherapy in the treatment of lung cancer is also promising.

SCLC accounts for about 15% of all lung cancers. It is the most strongly associated with cigarette smoking and typically occurs adjacent to the central airways with extensive lymphadenopathy and distant metastasis at diagnosis. Imaging commonly shows a large mediastinal mass that encompasses lymph nodes with an uncertain primary site of origin (**Figure 21**). Paraneoplastic syndromes are most commonly associated with SCLC, including hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone secretion (rare in other lung tumors), hypertrophic pulmonary osteoarthropathy (**Figure 22**), inflammatory myopathies, Cushing syndrome caused by ectopic adrenocorticotropic hormone secretion, and other hematologic and neurologic syndromes.

KEY POINTS

- There are two major classes of lung cancer: non–small cell lung cancer and small cell lung cancer; non–small cell lung cancer accounts for 80% of lung cancers and is divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.
- Testing for epidermal growth factor receptor mutation, anaplastic lymphoma kinase receptor tyrosine kinase translocation, and ROS proto-oncogene 1 receptor tyrosine kinase translocation is recommended in advanced-stage adenocarcinoma or mixed cancers.

Risk Factors

The main risk factor for lung cancer is smoking tobacco (voluntary or secondhand). This risk increases based on the number of pack-years of smoking and other carcinogenic exposures. Any reduction in lung cancer mortality will be linked to an overall reduction of cigarette smoking. Other risk factors that have been associated with lung cancer include previous radiation therapy, exposure to environmental toxins (asbestos, radon, metals, and diesel fumes), pulmonary fibrosis, HIV infection, family history of lung cancer, and alcohol abuse.

Screening

Until recently, screening for lung cancer was not widely performed, as previous studies had not shown that early detection resulted in any mortality benefit for lung cancer. The National Lung Screening Trial demonstrated a 20% reduction in lung cancer mortality in heavy smokers who were screened annually for 3 years. As a result, the U.S. Preventive Services Task Force has given annual lung cancer screening in high-risk patients a grade B recommendation. Screening should be performed in patients aged 50 through 80 years who have no symptoms of lung cancer and at least a 20-pack-year smoking history and who are current smokers or have quit within the last 15 years. Cessation of screening is recommended once a person has not smoked for 15 years and in those with limited life expectancy or those who would not be candidates for or willing to undergo surgery.

KEY POINT

- The U.S. Preventive Services Task Force recommends annual lung cancer screening using low-dose CT scan for those who are aged 50 to 80 years and have at least a 20-pack-year smoking history and who are either current smokers or have quit smoking within the last 15 years.

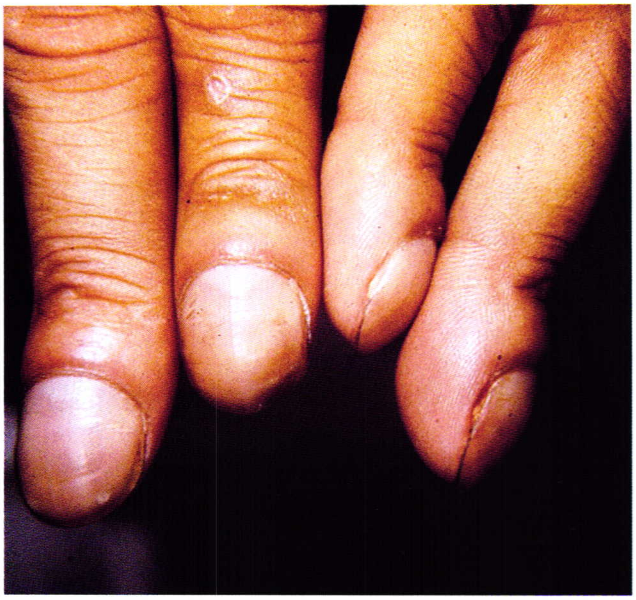


FIGURE 22. Clubbing is a part of the triad of the paraneoplastic syndrome hypertrophic pulmonary osteoarthropathy (HPOA). The other features of HPOA are periostitis of long bones and a painful polyarthritis.

TABLE 35. CT Findings Suggestive of Lung Malignancy

Irregular or spiculated borders
Upper-lobe location
Thick-walled cavitation
Solid component within a ground-glass lesion
Detection of growth on follow-up imaging

Diagnosis and Staging

When evaluating a patient who has a lung nodule or mass for possible lung cancer, two questions must be answered: first, what is the cell type? And second, what is the stage?

Initial evaluation should start with a full history, physical examination, complete blood count, serum chemistries, and CT scan of the chest. Most lung cancers present at a late stage. Symptoms result from the local effects of the tumor, metastatic spread involving other organs, or paraneoplastic syndromes. The most common symptoms at presentation include cough, dyspnea, chest pain, weight loss, and hemoptysis. NSCLC and SCLC present with similar symptoms. Similarly, the presence of findings on physical examination (consolidation, effusion, bone tenderness, neurological findings) will indicate advanced disease. CT scan findings that are suggestive of malignancy are listed in **Table 35**. PET scans can be very helpful in the initial evaluation of potential lung cancer, as several studies have demonstrated that PET identifies unsuspected mediastinal involvement, distant disease, or both, which informs staging biopsies and reduces futile (noncurative) surgery. The sensitivity of a PET scan to detect lung cancer is affected by the mass of the nodule and its metabolic rate, with increased potential for false-negative results for cancers smaller than 1 cm and slow-growing cancers, such as carcinoid tumors.

The definitive diagnosis of lung cancer requires tissue histopathology. In patients with radiographic evidence of advanced-stage disease, diagnosis and staging are best accomplished with a single invasive test at a location that will establish both the diagnosis and the stage of disease. Because there are many techniques available for tissue diagnosis, the strategy will depend on the size and location of the tumor, patient characteristics, and local expertise. In general, mediastinal and central lesions are best approached with bronchoscopy and smaller peripheral lesions are best approached with a transthoracic needle aspiration.

Definitive staging of lung cancer is essential, allows for accurate prognostication, and serves as a guide for treatment decision making. NSCLC is staged on the basis of the TNM staging system, taking into account the characteristics of the primary tumor (T), regional lymph node involvement (N), and metastatic disease (M).

SCLC is generally staged as either "limited" or "extensive" disease. Limited disease is defined as disease limited to one hemithorax and ipsilateral supraclavicular lymph nodes. The presence of disease outside these locations defines extensive stage disease.

Treatment of lung cancer is discussed in MKSAP 19 Oncology.

KEY POINTS

- The definitive diagnosis of lung cancer requires tissue histopathology.
- In patients with radiographic evidence of advanced-stage lung cancer, diagnosis and staging are best accomplished with a single invasive test at a location that will establish both the diagnosis and the stage of disease. **HVC**

Other Pulmonary Neoplasms

Carcinoid tumors are low-grade neoplasms comprised of neuroendocrine cells; they account for 1% to 2% of all lung cancers. Smoking is not a risk factor. Arising in the proximal airways, the predominant symptoms or signs are those of an obstructing mass (cough, dyspnea, monophonic wheezing) or bleeding. Bronchial obstruction may cause lobar atelectasis and recurrent episodes of pneumonia in the same pulmonary segment or may be asymptomatic (**Figure 23**). Misdiagnosing carcinoid tumors as asthma or pneumonia is responsible for delayed diagnosis. Lung carcinoid tumors are rarely associated with carcinoid syndrome. Surgical resection is often curative, and 10-year survival rates are higher than 90%.

Adenoid cystic carcinoma is a salivary gland tumor that occurs in the lower respiratory tract and accounts for less than 1% of all lung cancers. Surgical resection is the preferred treatment. Hamartomas are the most common benign lung neoplasm. These rare lesions are a combination of cartilage, connective tissue, smooth muscle, fat, and respiratory epithelium. On imaging they tend to be smooth-bordered nodules, which may contain fat.

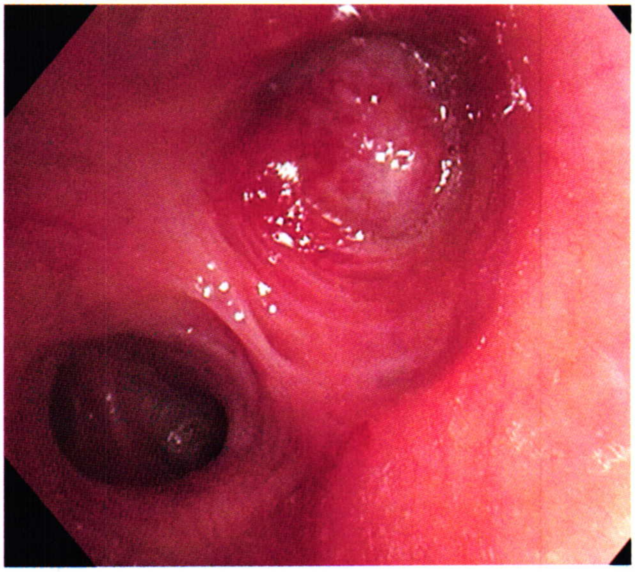


FIGURE 23. Endobronchial carcinoid can be seen on bronchoscopy as a smooth, polypoid, vascular-appearing mass that completely occludes a subsegmental airway of the right lower lobe.

The lung is a frequent site for metastatic disease from primary malignancies, which include head and neck, colon, kidney, breast, thyroid, and melanoma. Metastatic disease can present as solitary or multiple nodules; lymphangitic spread; and endobronchial, pleural, or embolic lesions. Surgical resection may be appropriate when a solitary pulmonary metastasis is identified without evidence of other metastatic disease.

KEY POINT

- Surgical resection of carcinoid tumors is often curative, and 10-year survival rates are higher than 90%.

Mesothelioma

Malignant pleural mesothelioma is a rare neoplasm that originates from the cells that line the pleural cavity (mesothelium). It can present as small nodules, plaque-like masses, or confluent sheets that can encase the lung. It is associated with inhalational exposure to asbestos fibers and has a latency of 20 to 40 years. In addition to malignant pleural mesothelioma and lung cancer, asbestos exposure has been linked to a spectrum of nonmalignant pleuropulmonary diseases (**Table 36**). Because of environmental control of asbestos, the rate of mesothelioma in the United States has been declining since 2000.

Patients with malignant pleural mesothelioma usually present with advanced disease. Symptoms include chest pain, dyspnea, cough, hoarseness, night sweats, or dysphagia. Clinical suspicion for malignant pleural mesothelioma should arise in the setting of pleural thickening or recurrent exudative pleural effusion and a history of asbestos exposure. The sensitivity of pleural fluid cytology is less than 5% and the diagnosis requires a pleural biopsy. Medical or surgical thoracoscopy has a greater than 90% sensitivity for malignancy. Treatment options depend on the extent of disease and patient factors and preferences and may include surgery, radiation therapy, and systemic chemotherapy. The overall prognosis of malignant pleural mesothelioma remains poor, with a median survival of 6 to 9 months.

KEY POINTS

- Mesothelioma is associated with inhalational exposure to asbestos fibers and has a latency of 20 to 40 years.

(Continued)

TABLE 36. Nonmalignant Asbestos-Related Pleural and Pulmonary Diseases

Disease	Characteristics
Asbestosis	Slowly progressive diffuse pulmonary fibrosis caused by inhalation of asbestos fibers
Benign asbestos pleural effusion	Small unilateral pleural effusion; may be associated with concomitant pleural plaques
Pleural plaques	Benign circumscribed areas of calcified pleural thickening with linear or nodular appearance

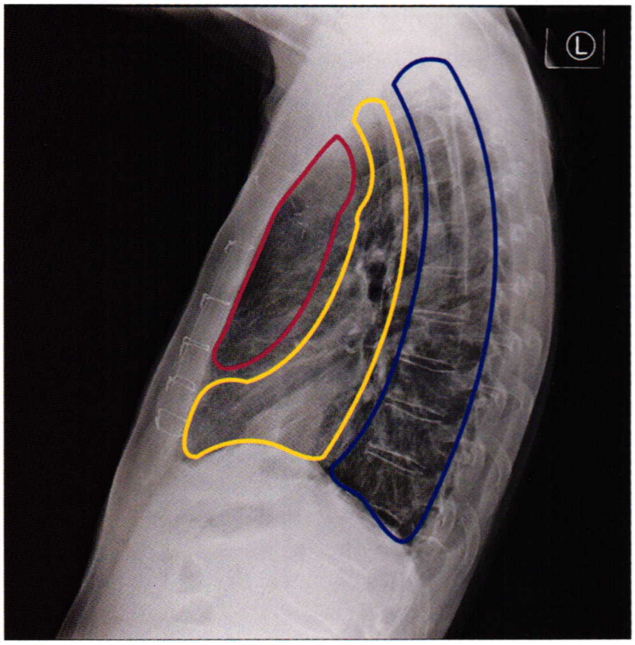


FIGURE 24. A lateral chest radiograph demonstrates the anterior (*red*), middle (*yellow*), and posterior (*blue*) mediastinal compartments.

KEY POINTS ***(continued)***

- Clinical suspicion for malignant pleural mesothelioma should arise in the setting of pleural thickening or exudative pleural effusion and a history of asbestos exposure.

Mediastinal Masses

The mediastinum is anatomically near the center of the thoracic cavity and is bound by the sternum anteriorly, the lungs and pleura laterally, and the vertebral column posteriorly. Tumors in the mediastinum can be either benign or malignant, and symptoms vary depending on size (mass effect) and systemic effects of the tumor. Dividing the mediastinum into compartments can be useful in developing a differential diagnosis when a mediastinal mass is discovered (**Figure 24**).

Anterior Mediastinum

The anterior mediastinal compartment lies between the posterior sternum and the great vessels and heart. It is the most common mediastinal location where malignant tumors occur. Masses in this location are usually remembered as the "terrible T's": thymoma, teratoma/germ cell tumor, "terrible" lymphoma, and thyroid. Thymic lesions are the most common and are associated with various paraneoplastic syndromes such as pure red cell aplasia and myasthenia gravis. Myasthenia gravis is an autoimmune disorder of the neuromuscular junction that commonly presents with muscular weakness, fatigability, ptosis, diplopia, and bulbar symptoms. Diagnosis can be confirmed with an acetylcholine receptor antibody test.

Middle Mediastinum

Masses in the middle mediastinum are common and are attributed to lymphadenopathy, cysts, esophageal disorders, or vascular lesions (aneurysm). Lymphadenopathy is most common and can be secondary to lymphoma, sarcoid, or metastatic disease.

Posterior Mediastinum

Masses in the posterior mediastinum include neurogenic tumors, meningoceles, and spine lesions. Neurogenic neoplasms are most common and are classified on the basis of their neural origin.

KEY POINTS

- Thymic lesions are the most common tumor in the anterior mediastinum and are associated with various paraneoplastic syndromes such as pure red cell aplasia and myasthenia gravis.
- Lymphadenopathy is the most common mass in the middle mediastinum and can be secondary to lymphoma, sarcoid, or metastatic disease.
- Neurogenic neoplasms are the most common tumors in the posterior mediastinum and are classified on the basis of their neural origin.

Sleep Medicine

Sleep disorders have six classifications: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders (including restless leg syndrome). For a discussion of insomnia, see MKSAP 19 General Internal Medicine 1.

Excessive Daytime Sleepiness

Excessive daytime sleepiness refers to difficulty staying awake and alert during daytime hours. Lack of self-recognition is common and poses a safety hazard if sleepiness occurs while driving or operating machinery. Sleepiness, a cardinal symptom of many sleep disorders, is different from fatigue, which is a lack of energy or sense of exhaustion that prevents mental or physical activity at the desired intensity or pace. Fatigue is unlikely to be solely attributable to a sleep disorder and is more likely to occur in other medical conditions.

Causes of excessive daytime sleepiness can be categorized as extrinsic (circumstantial) or intrinsic (disease-related) processes (**Table 37**).

TABLE 37. Extrinsic and Intrinsic Causes of Excessive Daytime Sleepiness

Extrinsic Causes
Insufficient sleep duration (or inadequate opportunity for sleep)
Circadian rhythm disturbance (shift work sleep disorder, jet lag)
Drug-, substance-, psychiatric-, or medical condition–related hypersomnia
Environmental sleep disorder (ambient noise, pets)
Intrinsic Causes
Sleep-disordered breathing syndromes, such as obstructive sleep apnea and central sleep apnea
Narcolepsy
Idiopathic hypersomnia
Restless leg syndrome and periodic limb movement disorder
Circadian rhythm sleep disorders (misalignment of the intrinsic circadian timing with the desired sleep schedule; for example, dementia and blindness)

Sleepiness can occur acutely when a person is deprived of the 7 to 8 hours of sleep most adults require. Functional impairment resulting from an inadequate amount of sleep is termed insufficient sleep syndrome. It likely is the most common cause of excessive daytime sleepiness and has been associated with cardiovascular disease and metabolic disorders such as glucose intolerance and obesity.

The initial evaluation of excessive daytime sleepiness should include a thorough history to assess the time available for and time spent sleeping before pursuing additional testing. Patients should be questioned about sleep hygiene, the effect of sleepiness on activities, sleep times and duration, sleep environment, napping, caffeine use, and duration of symptoms. In addition, physicians should probe for symptoms of specific sleep disorders (snoring, apneas, leg discomfort, and sleep attacks). A 1- or 2-week diary of the sleep-wake schedule is a simple tool that promotes self-realization of suboptimal sleep habits. A more objective assessment of sleep and wakefulness can be obtained with a wrist actigraph—a device that measures movement and ambient light during a period of 1 or 2 weeks. Wrist-worn consumer fitness products using similar technology may provide useful feedback. Questionnaires such as the Epworth Sleepiness Scale can quantify sleepiness and help gauge the response to treatment.

Objective sleep testing, either in-lab or at-home multichannel recordings, is often indicated when a primary sleep disorder is suggested by the history and physical examination. In certain cases, a multiple sleep latency test—a sleep laboratory–based study that measures the time to sleep during a series of daytime nap opportunities after a normal night of sleep—provides an objective measure of sleepiness and is key to establishing the diagnoses of narcolepsy and idiopathic hypersomnia.

All patients with excessive daytime sleepiness should be counseled about the dangers of drowsy driving and the need to maintain a routine sleep-wake schedule that allows for 7 to 8 hours of sleep per night. Specific treatment depends on the underlying condition. Short-term management of the occasional bout of acute sleepiness may include strategically timed naps or caffeine.

KEY POINTS

- The initial evaluation of excessive daytime sleepiness should include a thorough history to assess the time available for and time spent sleeping before pursuing additional testing.
- All patients with excessive daytime sleepiness should be counseled about the dangers of drowsy driving and the need for 7 to 8 hours of sleep per night.
- Functional impairment resulting from chronic sleep debt resulting from an inadequate amount of sleep is termed insufficient sleep syndrome; it likely is the most common cause of excessive daytime sleepiness.

Conditions that Disrupt Circadian Rhythm

Jet Lag

Jet lag results when the internal circadian clock is out of phase with the local time after air travel across multiple (typically more than three) time zones. Symptoms occur within one to two days after travel and may include insomnia, daytime sleepiness, and neuropsychiatric impairment. Eastward travel is more difficult to adapt to than westward travel. For short trips (one to two days), remaining on origin time might be preferable, if feasible. For longer trips, adjusting to the destination time may alleviate jet lag. Ways to promote adjustment include avoidance of sleep deprivation and dehydration, as well as bright light therapy starting up to 3 days before travel with the intention of advancing the circadian phase. In-flight hypnotic medications pose a risk for parasomnias (walking while asleep), particularly if alcohol is consumed. Postarrival measures include timed bright light exposure and melatonin, depending on the direction traveled, caffeine intake, and naps.

Shift Work Sleep Disorder

As much as one fifth of the American work force maintains a job schedule outside the usual day shift hours. Although some people acclimate well to this schedule, many experience excessive sleepiness, mood perturbations, and neurocognitive dysfunction. Symptoms persisting for at least 3 months meet the criteria for shift work sleep disorder. Management should first include counseling that takes into consideration eliminating shift work via a change in work schedule. If this is not feasible, then education about symptom management should be pursued. Interventions to improve daytime sleep may include bright light avoidance in the morning, maintaining a structured sleep-wake pattern (even during nonwork weeks), and use of melatonin, which is of modest benefit in shifting the physiologic sleep cycle. Hypnotic medications are of varying effectiveness and pose the risk for carryover effects into the nighttime work period. Interventions to promote nighttime wakefulness include bright light treatment in the evening before the night shift, caffeinated beverages, wake-promoting stimulants such as modafinil (only if conservative measures have failed), and planned napping during work breaks.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is defined by sleep interruption resulting from repetitive upper airway narrowing or collapse. These disordered breathing events, captured during sleep testing, are classified as either apneas (complete cessation of airflow for ≥10 seconds) or hypopneas (reductions in airflow), and when these events are divided by total sleep time they make up the apnea-hypopnea index (AHI). Although this frequency-based measure does not incorporate every important OSA outcome (for example, oxyhemoglobin desaturations), the AHI is probably the best composite metric of disease severity. An AHI of 5 to 14 per hour indicates mild OSA, 15 to 30 per hour indicates moderate OSA, and more than 30 per hour indicates severe OSA. The degree of sleepiness does not always correlate with the AHI.

KEY POINTS

- Obstructive sleep apnea is defined by sleep interruption resulting from repetitive upper airway narrowing or collapse.
- The apnea-hypopnea index is the total number of apnea and hypopnea events divided by total sleep time and can classify obstructive sleep apnea as mild (5-14 events per hour), moderate (15-30 per hour), or severe (more than 30 per hour).

Pathophysiology

With sleep onset, pharyngeal muscles acting to maintain upper airway patency relax, resulting in redundancy of the soft tissues that line the airway. Snoring is often a result of this process. The supine position promotes posterior displacement of the tongue, further narrowing the airway lumen. Disordered breathing events are most prominent during rapid eye movement, a stage of sleep characterized by atonia of nearly all muscles with the exception of the extraocular muscles and respiratory diaphragm. The process is terminated with a brief awakening from sleep (microarousal), during which upper airway patency is restored and ventilation resumes, typically followed by resumption of sleep and repetition of the process throughout the nightly sleep period.

Repetitive arousals and disruption of the sleep architecture contribute to the development of excessive daytime sleepiness and neurocognitive symptoms of OSA. Oxyhemoglobin desaturations can be profound, particularly in those with underlying cardiopulmonary disease. Current evidence suggests a causal link between OSA and systemic hypertension. However, relationships with other disorders such as heart failure, cardiac arrhythmias, diabetes mellitus, and mortality are merely associative.

Risk Factors

The most important risk factor for OSA is obesity, particularly in those with prominence of adipose tissue in the trunk and neck. The prevalence of OSA increases with age. Alcohol and sedative drugs can exacerbate OSA. Tonsillar hypertrophy, macroglossia, retrognathia and micrognathia, and upper airway mass lesions can contribute to upper airway narrowing.

KEY POINT

- The most important risk factor for obstructive sleep apnea is obesity.

Clinical Features and Diagnosis

Sleep-related choking or gasping is probably the most sensitive pretest indicator of OSA. Other symptoms include overnight awakenings, nocturia, morning headaches, and unrefreshing sleep. OSA may be clinically recognized for the first time after a procedure that entails general anesthesia or narcotics manifesting as repeated episodes of postoperative hypoxia or frank respiratory failure.

The most important established consequence of OSA is excessive daytime sleepiness. Collateral history from a family member as well as questionnaires such as the Epworth Sleepiness Scale can help identify excessive daytime sleepiness. Neuropsychiatric symptoms are common, including mood alterations, difficulty concentrating, and problems completing tasks at school or the workplace.

Objective testing is required for a diagnosis of OSA. Physical examination findings (crowded oropharynx, neck circumference) and questionnaires might increase pretest probability and guide decision-making about testing, but alone they are insufficiently sensitive or specific. Overnight pulse oximetry is also poorly discriminative, but in those who are asymptomatic with a low pretest probability, normal overnight oximetry might support the decision to avoid further testing. In-laboratory polysomnography is the gold standard test for mission-critical workers, patients with complicated OSA, and patients with comorbid conditions such as heart failure, neuromuscular disease, and advanced pulmonary disease in which diagnostic and treatment algorithms are more complex. Home sleep apnea testing, which is less costly and less resource intensive than polysomnography, is increasingly employed. Home sleep apnea testing does not measure electroencephalographic sleep like polysomnography does, but using respiratory tools or noninvasive measurements of vascular tone, pulse oximetry, and an accelerometer to detect posture, it is highly sensitive in diagnosing OSA in those with a pretest likelihood of moderate to severe disease. Home sleep apnea testing is less reliable in those felt to have milder disease.

KEY POINTS

- In-laboratory testing is recommended for mission-critical workers, patients with comorbid medical conditions, and patients with complicated obstructive sleep apnea.

(Continued)

KEY POINTS *(continued)*

- Home sleep testing may be most appropriate in patients without underlying cardiopulmonary or neuromuscular disease who have at least moderate to severe obstructive sleep apnea.

Treatment

The strongest indication for treatment of OSA is excessive daytime sleepiness, which generally improves with effective therapy. Neurocognitive and mood symptoms are probably indications for treatment. In patients who perform mission-critical work (truck drivers, pilots), the threshold for treatment may be lower than for others. The role of treatment in otherwise healthy or asymptomatic individuals is undecided. Several treatment options exist for OSA, the efficacy of which are generally based on the ability to reduce, if not abolish, apneas and hypopneas. Positive airway pressure therapy typically reduces the AHI toward zero by splinting open the upper airway. However, because the AHI does not always correlate with important outcomes in OSA, other treatments may adequately manage OSA for a given patient, even in the face of residual sleep apnea.

Positive airway pressure (and possibly oral appliances) has been shown to modestly reduce blood pressure in hypertensive patients with OSA, but the effect of treatment to manage comorbid cardiovascular disease or to prevent major cardiovascular events is thus far unproven. There is no effective pharmacologic treatment for OSA.

Weight Loss, Behavioral Modifications

OSA severity improves with weight loss. In minimally symptomatic patients with mild OSA, weight loss might be preferred therapy. Additional measures for mild OSA include reducing alcohol intake before bedtime, avoiding sedating medications, and avoiding a supine posture if OSA is position-dependent.

KEY POINT

- Obstructive sleep apnea severity improves with weight loss.

Positive Airway Pressure

Positive airway pressure remains the most effective therapy for preventing disordered breathing events, alleviating symptoms, and improving sleep-related quality of life in patients who have OSA. It acts by pressurizing the upper airway to maintain luminal patency.

The diagnosis by home sleep apnea testing is coupled to treatment with auto-adjusting positive airway pressure, which uses a computer algorithm to detect and overcome upper airway resistance in real time. Auto-adjusting positive airway pressure and continuous positive airway pressure are considered therapeutic equivalents in terms of reducing the AHI, improving adherence to treatment, and improving OSA symptoms. Bilevel positive airway pressure, which delivers separate inspiratory and expiratory pressures to augment alveolar ventilation, has no role in OSA without a hypoventilation syndrome.

The effectiveness of positive airway pressure therapy hinges on patient adherence. Educational programs can help, as can direct-to-patient reports wirelessly transmitted from the device to smartphones or computers. Adverse effects such as xerostomia and nasal dryness and congestion can be ameliorated by in-line humidification. Intranasal glucocorticoids or anticholinergics may be useful for recalcitrant nasal congestion or rhinitis. Modified pressure profiles that vary pressure over a respiratory cycle may enhance comfort. Proper mask fit enhances comfort and mitigates air leak.

KEY POINTS

- Positive airway pressure remains the most effective therapy for preventing disordered breathing events and alleviating symptoms in patients who have obstructive sleep apnea.
- Auto-adjusting positive airway pressure and continuous positive airway pressure are considered therapeutic equivalents for reducing the apnea-hypopnea index.

Oral Appliances

Oral appliances increase upper airway caliber primarily by exerting traction to advance the mandible. They do not reduce the AHI or increase oxygen levels as reliably as positive airway pressure, and they are generally avoided in more severe cases of OSA. However, these appliances have demonstrated good control of mild to moderate OSA and improvement in symptoms such as daytime sleepiness. Oral appliances may have a higher rate of adherence than continuous positive airway pressure.

Upper Airway Surgery

Although surgical procedures are generally not first-line therapy for OSA, maxillomandibular advancement significantly improves the AHI, even in severe disease, and can be considered for patients who do not benefit from or tolerate positive airway pressure therapy. Soft palatal procedures such as uvulopalatopharyngoplasty are of limited efficacy but may be an option in select patients. Tonsillectomy in adults may sometimes be effective, depending on the amount of extratonsillar soft tissue crowding the upper airway. Tracheotomy is an effective—although uncommonly used—treatment of OSA, limited by patient acceptance and aesthetics.

KEY POINT

- Surgical treatments for obstructive sleep apnea can be considered for patients who do not benefit from or tolerate airway pressure therapy.

Other Devices

A hypoglossal nerve stimulator been shown to improve the AHI in some patients. Implanted in the chest wall, it synchronizes with the respiratory cycle to contract the tongue muscles during inspiration. The patients who are most likely to benefit from this treatment are yet to be determined.

A nasal end-expiratory positive airway pressure device applied to the nasal openings via an adhesive has also been shown to reduce the AHI in some, but not all, patients. Supplemental oxygen is not recommended as primary therapy for OSA.

Central Sleep Apnea Syndromes

Classification and Pathophysiology

Central sleep apnea (CSA) syndromes are defined by pauses in airflow caused by loss of output from the central respiratory generators in the brainstem to the respiratory muscles, resulting in lack of respiratory effort. Under normal circumstances, a steady state exists in which ventilation maintains arterial P_{CO_2} in the normal range. In CSA syndromes, the response to arterial P_{CO_2} is exaggerated, resulting in ventilatory overshoot, hyperventilation, and reduction of the arterial P_{CO_2} to a level at which respiratory efforts cease. This central apnea further destabilizes ventilation and perpetuates the process. On polysomnography, central apnea is identified by the absence of respiratory effort associated with loss of airflow for at least 10 seconds.

KEY POINT

- Central sleep apnea syndromes are defined by pauses in airflow caused by loss of output from the central respiratory generators in the brainstem, resulting in lack of respiratory effort.

Risk Factors

Primary or idiopathic CSA, in which no risk factors are identified, is uncommon. Comorbid illnesses that predispose to instability of the ventilatory control system are the most common risk factors for CSA. The most prevalent association is between CSA and heart failure, which manifests as Cheyne-Stokes breathing, characterized by a crescendo-decrescendo pattern of ventilation. Atrial fibrillation, both in the setting of heart failure and in those with normal left ventricular systolic function, is a risk factor for CSA.

Known for their respiratory depressant effects in high doses, opioid analgesics are also associated with CSA. Opioids have destabilizing effects on ventilation, resulting in CSA and a chaotic breathing rhythm.

Approximately 10 percent of patients with OSA treated with positive airway pressure exhibit "treatment-emergent CSA," the significance of which is a matter of debate. In many, the central apneas dissipate as patients acclimate to positive airway pressure therapy.

Other risk factors for CSA include stroke, brainstem lesions, and possibly kidney injury. High-altitude periodic breathing is a form of CSA.

Symptoms and Diagnosis

It can be difficult to determine which symptoms are specific to CSA and which are associated with the comorbid condition or conditions. In-lab polysomnography is required to accurately diagnose CSA. It should also be noted that although the AHI is traditionally used to describe the severity of CSA, it has not been validated as a predictor of important clinical outcomes in CSA as it has been in OSA. Finally, abnormal oximetry does not reliably discriminate between OSA and CSA.

Treatment

Initial management of CSA should target modifiable risk factors. For example, reduction or elimination of opioids improves CSA. Medical optimization of heart failure has been shown to improve CSA and Cheyne-Stokes breathing, although it remains controversial as to whether CSA is an independent risk factor for worsened prognosis in those with heart failure.

Sleep-related symptoms probably represent an indication for treatment. Continuous positive airway pressure may occasionally be useful, especially in patients with overlapping OSA. Adaptive servo-ventilation is a form of positive airway pressure therapy that effectively suppresses CSA. However, a large trial showed an unexpected increase in mortality in patients with CSA and heart failure with reduced ejection fraction treated with ASV. Unlike OSA, oxygen during sleep may be indicated for patients with CSA who have hypoxia during sleep, as well as for those who cannot use or tolerate continuous positive airway pressure.

KEY POINT

HVC
- Initial management of central sleep apnea should target modifiable risk factors such as heart failure and elimination of opioids.

Sleep-Related Hypoventilation Syndromes

Sleep-related hypoventilation syndromes are associated with advanced COPD, obesity, and restrictive lung diseases, neuromuscular disorders, and other diseases (**Table 38**). These conditions are defined by impaired gas exchange during wakefulness further compromised with sleep, especially during the muscle atonia of rapid eye movement. Capnometry (measurement of either transcutaneous or end-tidal carbon dioxide levels) is increasingly used to confirm hypoventilation during sleep, although oxygenation criteria are also used to diagnose sleep-related hypoventilation syndromes. Sustained reductions in oxyhemoglobin saturation in the setting of a compatible medical condition signify a hypoventilation syndrome. Obstructive sleep apnea may or may not be an associated feature.

TABLE 38. Causes of Sleep-Related Hypoventilation Syndromes

- COPD
- Obesity hypoventilation syndrome
- Myxedema
- Neuromuscular disease
  - Muscular dystrophy
  - Amyotrophic lateral sclerosis
  - Myasthenia gravis
  - Guillain-Barré syndrome
  - Phrenic nerve injury
  - Poliomyelitis, post-polio syndrome
  - Cervical spine injury
- Respiratory depressant drugs (high-dose opioids)
- Kyphoscoliosis

KEY POINT

- Sleep-related hypoventilation syndromes are defined by impaired gas exchange during wakefulness further compromised with sleep; common associated conditions include advanced COPD, obesity hypoventilation syndrome, and restrictive lung diseases related to kyphoscoliosis or neuromuscular disorders.

Chronic Obstructive Pulmonary Disease

Patients with severe COPD often exhibit sleep-related hypoventilation. In addition to optimization of COPD therapy, supplemental oxygen is often used. The noninvasive pressure support of bilevel positive airway pressure can be used if hypercapnia is confirmed. In the overlap syndrome in which OSA is superimposed on COPD, continuous positive airway pressure therapy has been shown to decrease mortality rates.

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) results from a combination of the mechanical load on the respiratory pump and blunting of the ventilatory response to carbon dioxide. The hallmark of OHS is daytime hypercapnia, defined as a $\mathrm{P}_{\mathrm{CO}_2}$ greater than 45 mm Hg (5.9 kPa). OSA is usually but not always superimposed. Biventricular heart failure, pulmonary hypertension, and volume overload are common.

Weight loss is essential and consideration can be given to bariatric surgery. Positive airway pressure therapy is indicated. The American Thoracic Society recommends continuous positive airway pressure therapy for stable ambulatory patients diagnosed with OHS and concomitant severe OSA (AHI more than 30 events per hour). For hospitalized patients with suspected OHS-related respiratory failure, the American Thoracic Society recommends either bilevel positive airway pressure, with or without a backup respiratory rate, or volume-targeted pressure support. This therapy should be continued after hospital discharge until the patient can be evaluated with polysomnography and titrated with the appropriate positive pressure support. Supplemental oxygen may need to be added.

KEY POINT

- The hallmark of obesity hypoventilation syndrome is daytime hypercapnia, defined as an arterial P_{CO_2} greater than 45 mm Hg (5.9 kPa).

Neuromuscular Diseases

Noninvasive positive pressure ventilation devices are often prescribed to alleviate sleep-related symptoms and support blood oxygen levels in patients with neuromuscular disorders (**Table 39**). Bilevel positive airway pressure or volume-assured devices (average volume-assured pressure support), either with or without supplemental oxygen, are indicated once there is evidence of daytime hypercapnia indicative of chronic respiratory failure. Polysomnography may aid in optimizing machine and oxygen settings and in assessing concomitant sleep disorders, but it is not always needed. Tracheostomy and home mechanical ventilation are effective and may be appropriate for some patients. Supplemental oxygen may further depress ventilation in patients with respiratory muscle weakness and should generally not be prescribed without adjunctive ventilatory support, either by noninvasive means or by tracheostomy.

TABLE 39. Positive Airway Pressure Modes

Mode	Description	Indication
CPAP	Fixed pressure derived from an in-lab titration attended by a technician	OSA Occasionally CSA
APAP	Range of pressure delivered to maintain upper airway patency, determined by a proprietary computer algorithm	OSA
BPAP	Inspiratory pressure support delivered over and above a minimum expiratory pressure, derived from an in-lab titration	Hypoventilation syndromes OSA when CPAP fails (including patient intolerance)
Auto-BPAP	Range of bilevel pressures determined by a proprietary computer algorithm	Same as BPAP
ASV	Breath-by-breath adjustment of inspiratory pressure support and back-up rate determined by a proprietary computer algorithm; expiratory pressure set by a technician	CSA (including mixed CSA and OSA); do not use in patients with heart failure with reduced ejection fraction
Auto-ASV	Inspiratory and expiratory pressures determined by a proprietary algorithm	Same as ASV

APAP = auto-adjusting positive airway pressure; ASV = adaptive servo ventilation; BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CSA = central sleep apnea; OSA = obstructive sleep apnea.

KEY POINT

- Noninvasive positive pressure ventilation devices are often prescribed to alleviate sleep-related symptoms and support blood oxygen levels in patients with neuromuscular disorders.

High-Altitude–Related Illnesses

Pathogenesis of High-Altitude Illness

Diminishing barometric pressure associated with an ascent to altitude reduces the amount of ambient oxygen available for gas exchange, a condition known as hypobaric hypoxia. Physiologic responses to hypobaric hypoxia mechanistically underlie many disorders collectively referred to as high-altitude illness (**Table 40**). Susceptibility to high-altitude illness is individualized and difficult to predict. Although high-altitude illnesses can occur at all ages regardless of fitness level, patients with a history of high-altitude–related illness are at risk for recurrence. Other risk factors include rapid ascent (more than 3500 m in less than 2 days or more than 500 m per day above altitudes of 3000 m) and medical comorbidities that impair oxygenation, such as interstitial lung disease, COPD, and pulmonary hypertension. Acetazolamide and gradual ascent to altitude can be used prophylactically in patients who have previously suffered high-altitude illness or have other risk factors.

KEY POINT

- Acetazolamide and gradual ascent to altitude can be used prophylactically in patients who have previously suffered high-altitude illness or have other risk factors.

HVC

Acute Mountain Sickness

Cerebral blood flow and oxygen delivery to the brain are altered by the hypoxia and hypocapnia associated with the ascent to altitude. In acute mountain sickness—the most common high-altitude illness—symptoms are nonspecific and include headache, fatigue, nausea, and vomiting; disturbed sleep related to high-altitude periodic breathing is also common. Cerebral autoregulatory mechanisms can dampen the stress on blood flow, resulting in mild symptoms. Acute mountain sickness is estimated to affect as many as 25% of visitors to an altitude of 2000 m, the elevation at most major western U.S. ski areas. Heavy exertion and dehydration tend to amplify symptoms, which, provided there is no further ascent, typically resolve within 24 to 48 hours. Treatment and prevention approaches are shown in Table 40.

In high-altitude periodic breathing, chemoreceptors that are sensitive to hypoxia increase ventilation. This drives

TABLE 40. Spectrum of High-Altitude Illness Syndromes

High-Altitude Illness	Elevation Level	Symptoms	Treatment	Prevention
Acute mountain sickness	2000-2500 m	Nonspecific; include headache, malaise, anorexia, nausea, vomiting	Oxygen, acetazolamide, dexamethasone, descent from altitude, aspirin or NSAID for headache	Gradual ascent (<500 m/d) at high altitude; prophylaxis with acetazolamide or dexamethasone in rapid ascent or patients at high risk
High-altitude cerebral edema	3000-4000 m	Confusion, irritability, ataxic gait, coma, death	Descent from altitude, supplemental oxygen, hyperbaric therapy	Gradual ascent; consider acetazolamide or dexamethasone in patients at high risk
High-altitude pulmonary edema	>2500 m	Cough, exertional intolerance, dyspnea at rest (2-4 d after arrival at new altitude)	Supplemental oxygen and descent from altitude; adjunctive therapy: nifedipine, PDE-5 inhibitors Diuretics and nitrates not recommended Intubation may be required	Gradual ascent; consider nifedipine in patients at high risk

PDE-5 = phosphodiesterase-5.

arterial P_{CO_2} toward the apneic threshold and results in a pause in breathing (central apnea) when the threshold is crossed. With this pause, arterial P_{CO_2} eventually rises sufficiently to again stimulate breathing. The cycle of ventilatory overshoot, hypocapnia, and central apneas repeats at night. Patients complain of interrupted sleep and insomnia and may experience paroxysms of dyspnea that awaken them. Alcohol ingestion, which promotes dehydration, can intensify the sequelae of high-altitude periodic breathing.

KEY POINT

- Symptoms of acute mountain sickness are nonspecific and include headache, fatigue, nausea, and vomiting; disturbed sleep related to high-altitude periodic breathing is common.

High-Altitude Cerebral Edema

When the cerebral compensatory pathways are overwhelmed, severe, life-threatening cerebral edema can ensue. High-altitude cerebral edema is a feared manifestation of acute mountain sickness that tends to occur at higher elevations (above 3000 m). Recognition of cerebral edema mandates immediate intervention. Definitive treatment is immediate descent from altitude, particularly when the patient is still ambulatory, because incapacitation at high altitude exponentially complicates evacuation.

KEY POINT

- Definitive treatment of high-altitude cerebral edema is immediate descent from altitude, particularly when the patient is still ambulatory, because incapacitation at high altitude exponentially complicates evacuation.

High-Altitude Pulmonary Edema

The pulmonary vasculature constricts in response to hypoxia, resulting in increases in pulmonary vascular resistance. An exaggerated increase in pulmonary artery pressure is associated with high-altitude pulmonary edema. High-altitude pulmonary edema is uncommon but can be life-threatening. Patients are often tachypneic and tachycardic, and crackles or wheezing can be heard on chest examination. Pink, frothy sputum or frank hemoptysis may occur, which heralds worsening gas exchange and respiratory failure. The treatment of choice is supplemental oxygen along with rest, both of which will acutely reduce pulmonary artery pressures. Descent from altitude should be considered. See Table 40 for other adjunctive therapies.

Air Travel in Pulmonary Disease

The principles of hypobaric hypoxia also apply to commercial airline travel. Cabins are pressurized to the equivalent of 1500 to 2500 m (approximately 5000-8000 ft) in altitude, resulting in an inspired oxygen tension between 110 and 120 mm Hg (about 70% of the levels encountered at sea level). The resultant arterial P_{O_2} of approximately 60 mm Hg (8.0 kPa) is adequate for healthy individuals, but those with underlying pulmonary disease are at risk for significant hypoxemia during flight (**Table 41**).

TABLE 41. Risk Factors for Air Travel in Pulmonary Disease

Risk Factor
Advanced COPD complicated by hypercapnic respiratory failure
Pulmonary hypertension
Restrictive lung disease
Recent exacerbation of chronic lung disease
History of previous in-flight symptoms

TABLE 42. Preflight Screening in Chronic Lung Disease

Oxygen Saturation[a]	Recommendation
<92%	In-flight oxygen (typically 2-3 L/min)
92%-95%	Hypoxia altitude simulation testing
Already receiving long-term oxygen	Double flow rate during flight

[a] By pulse oximetry at sea level.

The risk for pneumothorax in air travel is low, as airline cabins are pressurized. In patients with chronic lung disease (such as asthma or COPD), signs or symptoms indicative of a pneumothorax (acute chest pain, dyspnea) should prompt the in-flight administration of supplemental oxygen, which promotes resorption of pleural air. For patients with chronic lung disease associated with hypoxia, preflight evaluation to determine recommended oxygen use is helpful (**Table 42**).

After cardiothoracic surgery, a delay of 3 to 4 weeks before air travel is reasonable. An existing pneumothorax has traditionally been considered a contraindication to flight because of the potential risk for expansion and tension physiology. Air travel may be safe in the presence of a small postoperative pneumothorax that has been radiographically stable.

KEY POINTS

- Pulse oximetry is a useful screening tool for patients who have chronic lung disease, with which an oxyhemoglobin saturation of less than 92% at sea level indicates a likely need for in-flight supplemental oxygen.
- HVC During air travel, doubling the flow rate is typically adequate for patients who are already receiving long-term supplemental oxygen.

Critical Care Medicine: ICU Utilization

Recognizing the Critically Ill Patient

There are no commonly accepted criteria for admission to an ICU. Signs and symptoms of clinical instability, including hypotension, hypoxemia, arrhythmias, and changes in mental status, may be useful in identifying patients who require intense resources or may be at risk for deterioration. Several scoring systems, such as the Acute Physiology and Chronic Health Evaluation, the Sequential Organ Failure Assessment, and the Simplified Acute Physiology Score, have been designed to help classify the severity of disease of patients admitted to the ICU. These scoring systems use vital signs and risk factors such as chronic disease, emergent surgery, and immunosuppression to calculate risk for mortality. Although they are rarely, if ever, used as ICU admission criteria, they are used to compare disease severity, progression, and outcomes. Disease-specific scoring systems can also be used to triage patients on the basis of risk for deterioration or death. Examples include the simplified Pulmonary Embolism Severity Index, the quick Sequential Organ Failure Assessment for sepsis, and the Pneumonia Severity Index or the CURB-65 for predicting mortality in community-acquired pneumonia. The electronic medical record databases are being harnessed to provide warning and predictive systems based on usually collected data (vital signs, age, and current or trending clinical information) to identify at-risk patients. Predictive models are evolving with the application of machine learning and artificial intelligence, yet their application remains at local levels and is not widespread.

Organization of Critical Care

To improve early management and resuscitation of patients who are at risk or deteriorating, many health care systems have developed rapid response teams or medical emergency response teams, with the aim of recognizing patients promptly, triggering early evaluation and management, and moving the patient to a higher level of care. A key element of this system is the ability for any member of the health care team or family member to trigger the rapid response team. Systematic reviews and meta-analyses of the effectiveness of these teams demonstrate a variable decrease in cardiac and respiratory arrests, unexpected deterioration, and mortality in adults.

Determining admission to a critical care bed is more complicated than simply assessing the level of patient illness. It is determined in a significant way by hospital and unit policies and resources unique to each institution. No standard admission model exists, although international societies have published guidelines. Hospitals have developed institution-specific protocols to better manage patients who require life-support technology.

An ICU is equipped with technology that allows continuous patient monitoring and delivery of life-sustaining interventions such as mechanical ventilation and emergency extracorporeal organ support. Hospital units designated as ICUs typically have the sickest patients and require nurse-to-patient ratios of 1:1 or 1:2, whereas a progressive care unit (also called an intermediate, transitional, or step-down unit) may have a nurse-to-patient ratio as high as 1:5, reflecting patients with lower acuity.

Critical care is generally defined as open unit versus closed unit and low-intensity versus high-intensity. In an open unit, patients are managed by their primary hospital team, which may or may not include a critical care consultant. Patients in a closed unit are managed primarily by the critical care team. Low-intensity units are open units. Although high-intensity units can be open or closed units, the critical care team is present throughout the day, providing consultation. Data supporting high-intensity and closed models with continuous staffing of ICUs by intensivists have been conflicting;

recent data, however, show a mortality benefit with the closed ICU.

The nature of the intensive care unit requires an interprofessional and multidisciplinary team. Key features that allow the best team dynamics are the explicit recognition of the roles and responsibilities of the team members, the use of shared communication models, and an environment of psychological safety.

KEY POINTS

- Rapid response teams have been shown to decrease the incidence of cardiac and respiratory arrests as well as hospital mortality in adults.
- **HVC** Data supporting high-intensity and closed models of critical care with continuous staffing of ICUs by intensivists have been conflicting; recent data, however, show a mortality benefit with the closed ICU.

Principles of Critical Care

Comprehensive Support of Critically Ill Patients

Critical care teams often include pharmacists, respiratory therapists, physical or occupational therapists, advanced practice providers, case managers, and social workers in addition to nurses and physicians. The goals of care are generally to restore health and allow the patient to return home while minimizing time in the hospital, medical complications, and long-term effects of critical illness. In cases of overwhelming or irreversible disease, goals of care may change to providing comfort and dignity at the end of life.

Patients in the ICU are at risk of developing many hospital-acquired conditions. The most common are health care–associated infections, skin and soft tissue pressure injury, malnutrition, gastrointestinal bleeding, delirium, and weakness (see MKSAP 19 Infectious Disease for information on health care–associated infections). Protocolized care can improve safety and decrease the incidence of these conditions.

Protocols used in the ICU should be evidence-based and periodically reviewed to ensure accuracy. For instance, stress ulcer prophylaxis with acid suppression has been standard practice for all patients receiving mechanical ventilation. Randomized trials evaluating acid suppression compared with placebo in patients who are at risk found decreased incidence of clinically significant bleeding, but no difference in mortality. There was no difference in the incidence of pneumonia or *Clostridioides difficile* infection. To this effect, practice guidelines give a weak recommendation to stress ulcer prophylaxis in those at high risk (i.e., patients with coagulopathy or chronic liver disease or who are receiving mechanical ventilation).

The complexity of disease and interventions in a critically ill patient requires a methodical approach to daily care such as the organ system–based approach, which allows caregivers to review the main disease process, affected organs and systems, and related interventions.

Sedation and Analgesia

ICU patients often require sedation and analgesia. The need for analgesia should be monitored at least every 4 hours. Pain should be assessed using an objective scale. **Table 43** outlines current guideline recommendations for analgesia and sedation, emphasizing multimodal therapy to manage pain. Opiates remain the mainstay, yet concurrent interventions can reduce medication doses and improve pain control. Preemptive analgesia should be provided for painful procedures (e.g., arterial line, thoracostomy tubes).

Sedation is commonly needed during invasive mechanical ventilation. Similar to analgesia, it requires monitoring and should be objectively assessed using a scale (e.g., Richmond Agitation Sedation Scale). Guidelines favor light sedation, often achieved with intermittent use of opiates. In patients who require continuous sedation, propofol or dexmedetomidine are preferred to benzodiazepines (associated

TABLE 43. Summary of Analgesia and Sedation Recommendations for Critical Care Patients

Analgesia Recommendations
Nonpharmacologic
Music therapy
Local cold therapy for procedures
Massage therapy
Daily sedation interruption
Relaxation therapy
Involve family
Pharmacologic
Opiates remain as the mainstay therapy
Multimodal therapy (nonpharmacologic and nonopiate)
Consider opiate reduction strategies
Adjunct acetaminophen
Adjunct low-dose ketamine for postsurgical patients
Adjunct gabapentin, carbamazepine, or pregabalin for nonneuropathic pain
Preprocedural pain management with opiate or NSAID
Sedation Recommendations
Use light sedation rather than deep sedation in mechanically ventilated patients
Use sedation protocols
Nurse-driven protocol
Daily sedation interruption
Favor use of propofol or dexmedetomidine over benzodiazepines
Use an objective scale to titrate sedation
Use a bispectral index monitor to assess sedation when scales cannot be used (e.g., neuromuscular blockers)

Data from Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46:e825-e873. [PMID: 30113379] doi:10.1097/CCM.0000000000003299 with increased delirium). An evidence-based practice for correction of oversedation is to stop the drug until the level of sedation is appropriate and then restart it at half the previous dose.

Interruption of Sedation and Analgesia

Daily protocolized interruption of sedation and analgesia in critically ill patients is associated with decreased length of mechanical ventilation, length of ICU stay, and incidence of delirium, although possibly no difference in 90-day mortality. Protocolized light sedation has shown similar patient outcomes to daily sedation interruption.

Delirium

Delirium is characterized by an acute change in cognitive functioning over hours to days, with fluctuations during the course of the day. Features of delirium include inattention, disorganized thinking, executive dysfunction (difficulty with problem solving), altered level of consciousness (lethargy or hypervigilance), perceptual disturbances (hallucinations or delusions), altered psychomotor activity (hyperactivity, hypoactivity, or both), sleep-wake disturbances, and labile mood. Delirium is extremely common in ICU patients and is associated with increased length of ICU stay, morbidity, mortality, and post–intensive care cognitive impairment. Risk factors for delirium include exposure to benzodiazepines, blood transfusion, preexisting dementia, older age, previous coma, pre-ICU surgery or trauma, and high severity of illness on ICU admission. Patients should be monitored and assessed using scales such as the Confusion Assessment Method-ICU or Intensive Care Delirium Screening Checklist. Measures to decrease delirium include early mobilization, preservation of nocturnal sleep, adequate pain management, orientation of the patient, removal of vascular and urethral catheters, provision of visual and hearing aids, and minimization of nonessential medications. Early mobilization in the earliest days of critical illness can be effective for treating and preventing delirium. Large randomized studies have failed to demonstrate the effectiveness of any medication to prevent or treat delirium. Use of antipsychotics are controversial, with no conclusive evidence of benefit. Benzodiazepines should not be used unless they are needed to treat alcohol withdrawal or seizures. Treatment involves identification and correction of the underlying cause, multicomponent bundled interventions (**Table 44**), and maintaining adequate nutrition and hydration. For further discussion of delirium, see MKSAP 19 Neurology.

TABLE 44. ABCDEF Care Bundle for Managing Delirium in the ICU

A:	**A**ssess, prevent, and manage pain
B:	Perform **B**oth SAT and SBT
C:	**C**hoice of sedation and analgesia
D:	**D**elirium: assessment, prevention, and management
E:	**E**arly mobility and exercise
F:	**F**amily engagement and empowerment

SAT = spontaneous awakening trial; SBT= spontaneous breathing trial.

KEY POINTS

- Sedation and analgesia should be monitored using objective standardized scales.
- Benzodiazepines should not be used for treating delirium unless they are needed to treat alcohol withdrawal or seizures. **HVC**

Nutritional Support

Malnutrition in critically ill patients leads to increased morbidity and mortality. All patients in the ICU should have a nutritional evaluation. Enteral nutrition should start within 24 to 48 hours of admission. Early enteral nutrition is associated with a decrease in mortality and infections. Enteral nutrition is preferred unless a contraindication is present (e.g., perforation, hemorrhage). Patients receiving vasopressors, neuromuscular blockers, hypothermia, or extracorporeal life support should receive enteral nutrition as soon as they can tolerate it. Critically ill patients who cannot maintain volitional nutritional intake should be fed as soon as possible using a gastric tube, large-bore tube, small-bore tube, or postpyloric tube. Guidelines recommend postpyloric feeding when a high risk for aspiration exists, but delays in placing a postpyloric tube should not delay initiation of enteral nutrition. Routine measurement of gastric residuals is not recommended because it delays achievement of feeding goals, increases the risk of clogging the enteral access, and may increase the risk for aspiration.

Guidelines recommend that supplemental parenteral nutrition should be considered only after 7 to 10 days of meeting less than 60% of energy and protein requirements by the enteral route alone. Adding parenteral nutrition to supplement enteral nutrition before this period may lead to harm and should be avoided. In contrast, parenteral nutrition should be started as soon as possible for severely malnourished patients, those at high risk for malnutrition, and those for whom enteral nutrition is not possible.

KEY POINTS

- Enteral nutrition is preferred and should be started within 24 to 48 hours of admission to the ICU.
- In nonmalnourished patients, supplemental parenteral nutrition should be considered only after 7 to 10 days of meeting less than 60% of energy and protein requirements by the enteral route alone.
- In patients receiving enteral feedings, measurement of gastric residuals is not recommended because it delays achievement of feeding goals, increases the risk of clogging the enteral access, and may increase the risk for aspiration. **HVC**
- Administration of parenteral nutrition to supplement enteral nutrition may lead to harm and should be avoided. **HVC**

Early Mobilization

Many factors contribute to weakness in critically ill patients, including immobility, disease, medications, and medical interventions. Immobility may result in muscular weakness, joint stiffness, pressure ulcers, osteoporosis, gastrointestinal dysmotility, and dysautonomia. Even a few days of immobility can have a prolonged effect on muscular strength; long-term follow-up of patients with critical illness demonstrates persistent weakness at 1 and 5 years. Mobilization and exercise are intuitive strategies to solve this problem, and although evidence is not yet conclusive, the risk/benefit analysis favors their application. Mobilization strategies consisting of interruption of sedation and physical and occupational therapy in the earliest days of critical illness are associated with decreased length of ICU stay and hospital stay, decreased days receiving mechanical ventilation, and improvements in quality of life and functional status.

KEY POINT

- The use of early mobilization strategies decreases length of time in the ICU and hospital and improves functional status and quality of life.

ICU Care Bundles

An ICU care bundle is a series of interventions that have been shown to improve patient outcomes when used together. Bundles can help clinicians monitor patients and guide appropriate interventions. Three care bundles that apply to critical care are summarized in **Table 45**.

High Value Care in the ICU

Critical care is responsible for a large proportion of U.S. health care costs. However, survival and quality-of-life outcomes are not that different from other top-economy countries. Societal, organizational, and payment pressures have encouraged a focus on providing high value care, defined as care that balances clinical benefit with cost and harm, with the goal of improving patient outcomes. The ICU is an environment in which high value care can have major effects, as the resources are expensive and the culture favors aggressive resource use. Internal medicine and critical care medical societies have joined the American Board of Internal Medicine Foundation's Choosing Wisely® campaign to promote cost-effective strategies that improve patient care and avoid waste and harm. In 2021 the Society of Critical Care Medicine's Choosing Wisely® recommendations (https://www.choosingwisely.org/societies/society-of-critical-care-medicine/) addressed the overuse of the following critical care practices: (1) retaining catheters and drains without a clear indication, (2) delaying discontinuation of mechanical ventilation, (3) continuing antibiotic therapy without need, (4) delaying mobilization of critically ill patients, and (5) providing care without ensuring that it aligns with patient preferences. The 2014 Choosing Wisely® list included a recommendation against daily routine laboratory testing.

TABLE 45. ICU Care Bundles

Ventilator-Associated Pneumonia[a]
Head of bed elevated at least 30 degrees
Daily sedation interruption and assessment of readiness to extubate
Endotracheal tubes with subglottic suction
Early exercise or mobilization for physical conditioning
Change ventilator circuits only if malfunctioning or visibly soiled
Central Line–Associated Bloodstream Infections[b]
Hand hygiene
Maximal barrier precautions
Chlorhexidine skin antisepsis
Avoid femoral access
Daily review of line necessity
Sepsis[c]
1-hour bundle:
Measure lactate level
Obtain blood cultures before antibiotics
Administer broad-spectrum antibiotics
Administer 30 mL/kg crystalloids for hypotension or lactate ≥4 mEq/L (4 mmol/L)
Use vasopressors if no response to fluids; keep MAP above 65 mm Hg

MAP = mean arterial blood pressure, calculated as [(2 × diastolic) + systolic]/3.

[a] Recommendations based on Klompas M, Branson R, Eichenwald EC, et al; Society for Healthcare Epidemiology of America (SHEA). Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35:915-36. [PMID: 25026607] doi:10.1086/677144

[b] Recommendations from the Institute for Healthcare Improvement.

[c] Recommendations based on Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign bundle: 2018 update [Editorial]. Intensive Care Med. 2018;44:925-928. [PMID: 29675566] doi:10.1007/s00134-018-5085-0

Respiratory Support

Admission to the ICU for respiratory insufficiency is prompted by three basic conditions: hypoxemic respiratory failure, hypercapnic respiratory (ventilatory) failure, and upper airway impairment.

Acute hypoxemic respiratory failure is caused by shunting (perfusion of lung units that are not ventilated) because of alveolar collapse or flooding with cells, fluid, or blood. Therapies for hypoxemia include increasing the inhaled oxygen concentration or applying positive end-expiratory pressure to open up flooded or collapsed alveoli.

Acute hypercapnic respiratory failure is caused by dead space (ventilation of poorly perfused lung units) or pump failure (inability to move air in and out of the lungs). Adequate ventilation requires sufficient pressure from the respiratory muscles to move air to the alveoli. The pressure generated has to overcome both elastic (chest wall and lung) and resistive (airway) forces. Ventilatory failure can result from elastic and resistive forces that are too high or respiratory muscles that are too weak. Mechanical ventilation (invasive or noninvasive) is the mainstay treatment for hypercapnia.

Upper airway impairment is usually a manifestation of either obstruction of the airway (e.g., angioedema) or inability to protect the airway (e.g., opiate intoxication). The management is to maintain a patent airway (e.g., endotracheal tube, tracheostomy, or cricothyrotomy) (see Common ICU Conditions).

Oxygen Therapy

Several devices deliver oxygen, each with different characteristics that serve patients differently. These devices are titrated most often to maintain a "normal" arterial oxygen saturation ($\text{Sa}o_2$) or pulse oximetry ($\text{Sp}o_2$). However, higher oxygen saturation is not always desirable. Evidence now suggests that supplementing oxygen for patients whose oxygen saturation is already 96% or higher actually increases mortality. Recommendations include both that an $\text{Sp}o_2$ of 96% or lower should be maintained in patients receiving oxygen therapy and that oxygen therapy should not be started for patients with acute myocardial infarction or stroke and an $\text{Sp}o_2$ of 93% or higher. These guidelines do not apply to all acute medical conditions. For example, higher $\text{Sa}o_2$ values are beneficial for patients with carbon monoxide poisoning (a specific case in which $\text{Sp}o_2$ may be unreliable and $\text{Sa}o_2$ should be used instead), cluster headache, sickle cell crisis, and pneumothorax.

High-Flow Nasal Cannula

High-flow nasal mixes and humidifies high-flow air and oxygen (30 L/min or more) to deliver a consistent $\text{F}io_2$ (0.21-1.0) through a nasal cannula. The high flow creates some positive airway pressure, but the amount depends on the flow rate and cannot be quantified. High-flow nasal cannula can decrease respiratory rate, work of breathing, and dead space. It has physiological and patient comfort appeal, but the evidence is developing. Systematic reviews have found no difference in hypoxemic events compared with other methods used to oxygenate critically ill patients before and during intubation. In managing acute hypoxemic respiratory failure, it may decrease the need for tracheal intubation, but it has no demonstrated effect on patient mortality. Current guidelines recommend high-flow nasal cannula because the reduced risk for intubation is important to patients. In the postextubation period, high-flow oxygen may reduce the risk for recurrent respiratory failure and reintubation. In high-risk patients (older than 65 years or with chronic heart or lung disease), high flow alone was less effective than high flow plus noninvasive ventilation immediately after extubation in preventing reintubation.

The initial application of high-flow nasal cannula should occur in the critical care setting with close monitoring for tolerance and effectiveness. In patients with acute hypoxemic respiratory failure who are receiving high-flow oxygen, the ROX index, defined as the ratio of $\text{Sp}o_2/\text{F}io_2$ (%) to respiratory rate (breaths/min), is a validated score that helps identify patients at low or high risk for intubation.

Mechanical Ventilatory Support: General Principles

Mechanical ventilator support for respiratory failure is accomplished by noninvasive positive pressure ventilation (NPPV), using a helmet, nasal, oral, or full-face mask, or invasive ventilation with an endotracheal tube or tracheostomy. Selection of NPPV or invasive ventilation is dependent on the clinical situation and the goals of treatment. Initiation of any form of mechanical ventilatory support should be performed in a monitored unit (emergency department or ICU).

Noninvasive Positive Pressure Ventilation

There are two types of NPPV: continuous positive airway pressure and bilevel positive airway pressure. Continuous positive airway pressure delivers a constant airway pressure during inspiration and expiration. Bilevel positive airway pressure delivers a higher level of positive airway pressure during inspiration than during expiration, thus providing additional inspiratory support and increased tidal volume. The support is titrated to an appropriate level of gas exchange and to optimize patient respiratory effort. **Table 46** highlights the physiologic effects and indications for these different modes of ventilatory support.

Indications and Patient Selection

Evidence favors the use of NPPV in the critical care setting in patients with COPD exacerbations, cardiogenic pulmonary edema, neuromuscular disease, or obesity hypoventilation syndrome and in patients at high risk of failing extubation (e.g., those >65 years old or with heart failure or COPD). However, NPPV also increases the risk for mortality in some patients, such as those with COPD exacerbations who failed NPPV and require subsequent intubation. All patients placed on NPPV need to be monitored and reevaluated within 2 hours to determine whether the therapy is effective and whether adjustments are needed.

There is evidence suggesting harm when intubation is delayed or when tidal volumes are too high because of NPPV. Contraindications to the use of NPPV include persistent altered mental status, increased airway secretions, emesis, gastric distention, airway obstruction, recent esophageal surgery, cardiac arrest, inability to protect the airway, facial trauma/surgery (including oral, nasal, or sinus), and patient intolerance of the mask.

Application

Proper mask sizing and patient adaptation to the device are essential; these require time and coaching of the patient. The timing of NPPV is very important, as late application (impending respiratory failure) is associated both with the need for subsequent intubation and with worse outcomes. After initiation, patients should be closely monitored for tolerance and adverse effects (patient comfort, skin integrity, gastric distention, and eye irritation), effectiveness of the ventilatory parameters (tidal volumes and respiration rate), and clinical

TABLE 46. Modes of Noninvasive Positive Pressure Ventilation

Mode	Function	Physiologic Effects	Indications
CPAP	Applies and maintains a constant airway pressure throughout the respiratory cycle	Maintains patent airway in the setting of obstructive sleep apnea, increases functional residual capacity, increases mean airway pressure	Obstructive sleep apnea Pulmonary edema Excessive dynamic airway collapse Preintubation Postextubation
BPAP	Applies two different levels of airway pressure: IPAP and EPAP	Same as CPAP, but also decreases work of breathing and augments tidal volume	COPD exacerbation Obesity hypoventilation syndrome Neuromuscular diseases Time-limited trial in selected "do not intubate" patients with clear goals of care
BPAP with S/T mode	BPAP with a minimum set respiration rate	In case of apnea, continues to deliver breaths	Hypoventilation, central apneas

BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; S/T = spontaneous/timed.

improvement (blood pH, respiration rate, oxygen saturation, and mental status).

Invasive Mechanical Ventilation

Invasive mechanical ventilation involves the use of an endotracheal tube or tracheostomy to deliver positive pressure ventilation. The indications for invasive mechanical ventilation are hypoxemic or hypercapnic respiratory failure, contraindication to NPPV, and inability to protect the airway. The timing, the ventilation mode, and the settings depend on disease and patient factors (**Table 47**).

The appropriate mode of invasive mechanical ventilation is chosen on the basis of mode characteristics that favor the prevailing clinical goal, based on the patient's disease and physiologic status. When safety is the priority, the settings focus on lung protective ventilation, meaning adequate minute ventilation and oxygenation while maintaining the lowest effective tidal volume and plateau pressure to prevent ventilator-induced lung injury (see Common ICU Conditions). Ventilator-induced lung injury can occur early or late in the course of ventilation and results from the overdistension of alveoli ("volutrauma") or the collapse of alveoli with expiration ("atelectrauma").

When patients are awake and the risk for lung injury has decreased, the prevailing goal becomes comfort. Patient-ventilator interaction should be optimized to provide comfort using a mode that allows synchrony and adequate support. Considerations include the patient's respiratory muscle weakness or fatigue, the presence of acidosis, and level of sedation.

Weaning

Patients should be liberated from mechanical ventilation as soon as possible. The concurrent use of daily awakening or targeted light sedation protocols and spontaneous breathing trials reduces mechanical ventilation time and mortality (**Table 48**). Daily spontaneous breathing trials assess the readiness to breathe unassisted. The current recommendation is to perform trials of at least 30 minutes and no more than 2 hours in length, using low levels of pressure support (≤8 cm H_2O) or a T-piece to identify patients who can be evaluated for extubation.

Synchronized intermittent mandatory ventilation is a mode of ventilation that combines mandatory and spontaneous breaths. It should not be used to wean patients from mechanical ventilation.

KEY POINTS

- Spontaneous breathing trials of from 30 minutes to 2 hours using low levels of pressure support (8 cm H_2O or less) can identify patients who may be evaluated for extubation.
- The use of NPPV immediately after extubation can prevent extubation failure in patients at high risk, such as those with heart failure, COPD, or hypercapnia.

Hemodynamic Support

Patients in the ICU sometimes require invasive tools for hemodynamic monitoring. These devices increase the risk for adverse events, so they should be used only when sufficient information cannot be obtained with noninvasive methods and should be removed as soon as possible. For example, routine use of pulmonary artery catheters does not lead to improved outcomes, is associated with increased complications, and may increase mortality.

Intravenous Access

There are several devices available to achieve central intravenous (IV) access. Use depends on many factors, including urgency, expected duration, and reason for access (**Table 49**). Peripheral venous access with a short, wide-bore catheter is the route of choice for rapid volume resuscitation. Removal of intraosseous

TABLE 47. Most Frequently Used Ventilator Modes

Common Name	Mode Classification	Breath Control Variable	Breath Sequence	Targeting Scheme	Characteristics
Volume control assist/control	VC-CMVs	VC: The ventilator controls the flow (volume) during the mandatory breath. If the patient's effort, lung compliance, or resistance changes, the ventilator will still deliver the set tidal volume.	CMV: All breaths are mandatory. The patient may or may not trigger the breath, but the ventilator always ends (cycles) the breath when the tidal volume is delivered.	Set-point, s: The operator sets all parameters of the breath (flow waveform, flow rate, and volume). The ventilator does not adjust to the patient's effort or change in lung characteristics.	Ensures minimum minute ventilation Ability to limit tidal volume delivered Least likely to allow comfort for patient because of limitation in flow Serves the goal of safety
Pressure control assist/control	PC-CMVs	PC: The ventilator controls the pressure during the mandatory breath. If the patient's effort, lung compliance, or resistance changes, the ventilator will still deliver the set inspiratory pressure (but the tidal volume delivered will change).	CMV: All breaths are mandatory. The patient may or may not trigger the breath, but the ventilator always ends the breath when the preset inspiratory time elapses.	Set-point, s: The operator sets all parameters of the breath (inspiratory pressure and inspiratory time). The ventilator does not adjust to the patient's effort or change in lung characteristics.	Ensures pressure will not rise above a set limit Tidal volume is dependent on patient effort, lung compliance, and resistance Serves the goal of safety (if tidal volume within range)
Pressure support, continuous positive airway pressure	PC-CSVs	PC: The ventilator controls the pressure during the breath.	CSV: All breaths are spontaneous. The patient triggers and cycles the breath.	Set-point, s: The operator sets all parameters of the breath (inspiratory pressure). The ventilator delivers the breath and does not adjust to the patient's effort or change in lung characteristics.	Patient determines size and timing of breaths Serves the goal of comfort, as it allows synchrony with patient Can be used to assess extubation readiness
Synchronized intermittent mandatory ventilation	PC-IMVs,s or VC-IMVs,s	PC or VC: The mandatory breaths can be set to be volume or pressure controlled, not both.	IMV: Preset mandatory breaths are delivered by the ventilator at a minimum set rate. Spontaneous breaths are permitted in between mandatory breaths. The triggering of the mandatory breath will be coordinated with the patient if the inspiratory effort occurs close to the scheduled time trigger.	Set-point, s: One "s" refers to the mandatory breath and the other to the spontaneous breath. Generally, all spontaneous breaths in IMV are pressure supported (PC-CSVs).	Provides a minimum set amount of mandatory breaths Allows spontaneous breaths Serves the goal of safety, as it allows a minimum minute ventilation

CMV = continuous mandatory ventilation; CSV = continuous spontaneous ventilation; IMV = intermittent mandatory ventilation; PC = pressure controlled; s = set-point; VC = volume controlled.

devices should be done within 24 hours of placement. In general, all IV access should be removed as soon as possible to decrease the risk for infection or thrombosis. Procedure-related complications, such as arterial injury, nerve injury, bleeding, or pneumothorax, can be minimized with the use of ultrasound-guided placement. Devices with lower risk for complications (e.g., peripheral IV access) should be prioritized whenever possible.

KEY POINTS

- All intravenous access should be removed as soon as possible to decrease the risk for complications.
- Peripheral intravenous access with a short, wide-bore catheter is the route of choice for rapid volume resuscitation.

TABLE 48. Common Criteria for Spontaneous Breathing Trials and Extubation[a]

Criteria to Perform SBT
Cause of respiratory failure improved
$FIO_2 \leq 40\%$ and PEEP $\leq$5-8 cm H_2O
pH >7.25
Hemodynamic stability
Able to spontaneously breathe
Criteria to Pass SBT—At Least 30 Minutes Without the Following:
Clinical evidence of respiratory distress
SpO_2 <90%
Respiration rate >35/min
New arrhythmias
Tachycardia
Hypotension or hypertension
Additional Considerations Before Extubation
Quantity of secretions: need for frequent suctioning
Adequacy of cough
Altered mental status

PEEP = positive end-expiratory pressure; SBT = spontaneous breath trial; SpO_2 = peripheral arterial oxygen saturation.

[a] These criteria may differ between institutions.

Blood Pressure Support

A mean arterial pressure of 65 mm Hg is considered the threshold at which there is sufficient pressure for organ perfusion in most humans. A study of higher (80-85 mm Hg) mean arterial pressures in patients with septic shock demonstrated no improvement in mortality. Blood pressure is usually monitored noninvasively with a blood pressure cuff. An arterial line for continuous monitoring may be more useful than cuff pressures when the systolic blood pressure is less than 90 mm Hg, when frequent measurements are needed (particularly for patients requiring continuous IV medication), or when the cuff readings are unreliable (in patients with morbid obesity, vascular anomalies of the extremities, or other anatomic features limiting cuff accuracy). Assessment of tissue perfusion includes physical examination (skin temperature, mottling, jugular venous distention), measurement of vital signs, and focused cardiac evaluation with tools such as echocardiography and invasive and noninvasive cardiac output monitors. These tools must be applied in the correct clinical scenario to minimize erroneous diagnostic results. Often, physical examination and vital signs alone are sufficient to make diagnostic conclusions. Management of hemodynamic perturbations should focus on the underlying cause of hypotension. For instance, hypotension resulting from deceased preload should be initially treated with volume resuscitation. Support of blood pressure may require the use of vasopressors (**Table 50**).

TABLE 49. Types of Central Venous Access

Type	Indications	Duration	Potential Complications	Contraindications
Peripherally inserted central venous catheter	Delivery of potentially caustic medications such as vasoactive agents, sedatives, or antibiotics; central venous access	A few days to 1 year	Low risk overall for pneumothorax; reduced infection risk compared with nontunneled catheter; risk for clot formation or occlusion resulting from smaller vessel diameter	Current or pending dialysis
Temporary nontunneled	Same as peripherally inserted central venous catheter; short-term dialysis, central venous pressure monitoring	Infection risk increased after 7 days	Infection, site-specific complications such as pneumothorax for subclavian or low internal jugular approach	
Long-term tunneled	Long-term TPN, chemotherapy, long-term antibiotics, dialysis; tunneled Dacron cuff or other fabric allows tissue adherence to reduce infection and dislodgement	More than 6 weeks	Infection, same risks as nontunneled catheter during placement	
Ports or totally implanted	Long-term intermittent access such as chemotherapy	More than 6 weeks	Lowest risk for infection, but more difficult to implant with more costs; hidden extravasation beneath skin	
Intraosseous (tibia or humeral head [adults])	When IV access otherwise not attainable in emergent setting	About 24 hours	Low risk for infection; flow rates may be slower; if pain with infusion, can use 2% preservative-free lidocaine injected slowly to control it	Do not place in a bone with a fracture, in a patient with a diagnosis of osteoporosis, or after a recent (24-48 h) intraosseous access attempt

IV = intravenous; TPN = total parenteral nutrition.

TABLE 50. Selection of Vasopressors and Inotropes

Medication	Type of Shock	Receptor Target	Primary Effect	Comments
Angiotensin II	Distributive	AT II	↑ SVR	Role still being defined; concern for increase in thrombotic events
Dobutamine (not a vasopressor)	Cardiogenic Distributive	β_1, β_2	↑ Inotropy	First choice for cardiogenic shock without hypotension Add-on therapy for distributive shock with depressed cardiac function
Dopamine (high-dose)	Cardiogenic	D, α_1, β_1	↑ SVR, ↑ inotropy	Associated with increased mortality compared with norepinephrine in distributive shock; use only in cases of severe bradycardia in septic shock
Dopamine (low-dose)	Cardiogenic	D, β_1	↑ Inotropy, ↑ HR	Not recommended to augment renal blood flow
Epinephrine	Cardiogenic Distributive Hypovolemic	α_1, α_2, β_1, β_2	↑ SVR, ↑ inotropy	First choice anaphylactic (distributive) shock May be added to norepinephrine in septic (distributive) shock
Norepinephrine	Cardiogenic Distributive Hypovolemic	α_1, α_2, β_1	↑ SVR, ↑ inotropy	First choice in cardiogenic, distributive, and hypovolemic shock
Phenylephrine	Distributive	α_1	↑ SVR	May be used when norepinephrine is contraindicated (tachyarrhythmias) or after failure of first-line drugs; may depress cardiac output by causing reflex bradycardia
Vasopressin	Distributive Hypovolemic	V	↑ SVR	May be added to norepinephrine in septic (distributive) shock; no role in other shock states

AT II = angiotensin type II; HR = heart rate; SVR = systemic vascular resistance.

Norepinephrine is the most commonly used agent and has been shown to reduce mortality. However, other agents are available and may be used in specific situations.

KEY POINT

HVC
- A mean arterial pressure of 65 mm Hg is considered the threshold at which there is sufficient pressure for organ perfusion in most humans.

ICU Complications

ICU complications may be classified as early (occurring during the hospitalization) or late (persisting after the critical illness).

ICU-Acquired Weakness

Between 25% and 100% of critically ill patients develop muscle weakness. Muscle weakness may result from complications involving the nervous system (critical illness polyneuropathy), the muscles themselves (critical illness myopathy), or some combination of both, or it may be nonspecific (ICU-acquired weakness). It may also be related to prolonged neuromuscular blockade. **Table 51** lists descriptions of types of ICU-acquired weakness. Identified risk factors include sepsis, multisystem organ failure, severe illness, prolonged immobility, and hyperglycemia. Evaluation for ICU-acquired weakness can initially be performed at the bedside, using the Medical Research Council muscle scale—however, electromyogram testing remains the gold standard. ICU-acquired weakness generally improves over weeks to months, but it may persist for years. Strategies to minimize ICU-acquired weakness include aggressive management of critical illness, early mobilization, and management of hyperglycemia.

KEY POINT

- Strategies to minimize ICU-acquired weakness include aggressive management of critical illness, early mobilization, and management of hyperglycemia.

Long-Term Cognitive Impairment

As many as 30% to 80% of patients with critical care illness develop long-term impairment in cognition, which manifests clinically as cognitive impairment. Observations have demonstrated that the level of impairment 1 year after critical illness is similar to mild Alzheimer disease. Although the specific risk factors and interventions related to developing cognitive impairment are not well defined, the development and duration of delirium during the ICU stay appear to be major predictors.

TABLE 51. Definitions and Characteristics of ICU-Acquired Weakness

ICU-Acquired Weakness
Clinically detected weakness with no explanation other than the critical illness
Proximal and distal symmetrical flaccid weakness with sparing of cranial nerves
Often failure to wean from mechanical ventilation is the first indication of weakness
Diagnosis of exclusion
Critical Illness Polyneuropathy
ICU-acquired weakness with electrophysiological evidence of axonal polyneuropathy
Quadriparesis or quadriplegia, decreased muscle tone, sparing of facial muscles; deep tendon reflexes decreased
Critical Illness Myopathy
ICU-acquired weakness with electrophysiological or histological evidence of myopathy
Examination is similar to critical illness polyneuropathy; new sensory loss is suggestive; creatinine kinase may be elevated
Critical Illness Neuromyopathy
Coexistence of critical Illness polyneuropathy and critical illness myopathy
Mixed features; perhaps most prevalent form
Prolonged Neuromuscular Blockade
Prolonged effects in patients with renal failure, liver failure, hypermagnesemia
Flaccid areflexic quadriplegia with cranial nerve involvement
Repetitive nerve stimulation shows decremental response

Post–Intensive Care Syndrome

Post–intensive care syndrome describes a group of symptoms that present in patients after an episode of critical care. The symptoms have been grouped according to the area that they affect (physical impairment, mental health, and cognitive impairments). Patients with post–intensive care syndrome have increased health care use, increased morbidity and mortality, and impaired quality of life. Post–intensive care syndrome also affects the caregivers and family of the patient; it has been reported that family members experience anxiety, depression, and posttraumatic stress disorder. Current research and interventions are focusing on how to improve recognition, prevention, diagnosis, and management.

Common ICU Conditions

Acute Respiratory Failure

Acute respiratory failure occurs when a patient cannot adequately oxygenate blood (hypoxemia) or remove carbon dioxide (hypercapnia) from the blood. History and physical examination together with tests such as chest radiograph (**Table 52**), CT scan, arterial blood gas, and pulse oximetry are useful as part of a structured evaluation allowing clinicians to identify and treat factors leading to respiratory failure. This approach includes evaluation for airway compromise, inadequate oxygenation, and inadequate ventilation (**Figure 25**).

TABLE 52. Radiographic Findings and Differential Diagnosis in Acute Respiratory Failure

Finding	Differential Diagnosis
No infiltrate	Asthma/COPD exacerbation
	Drug overdose/toxicity
	Intracardiac shunt
	Neuromuscular weakness
	Pulmonary embolus
Diffuse infiltrates	Acute respiratory distress syndrome
	Cardiogenic pulmonary edema
	Acute exacerbation of idiopathic pulmonary fibrosis
	Pneumonia
	Other (e.g., acute hypersensitivity pneumonitis, acute eosinophilic pneumonia)
Focal infiltrate	Airway obstruction
	Atelectasis
	Pneumonia
	Pulmonary infarction

Acute Upper Airway Management

In patients who cannot maintain a patent airway or protect themselves against aspiration, a cuffed endotracheal or tracheostomy tube should be placed. An oropharyngeal, nasopharyngeal,

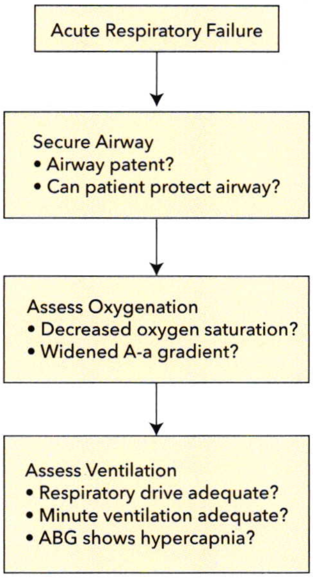

Acute Respiratory Failure
Secure Airway
• Airway patent?
• Can patient protect airway?
Assess Oxygenation
• Decreased oxygen saturation?
• Widened A-a gradient?
Assess Ventilation
• Respiratory drive adequate?
• Minute ventilation adequate?
• ABG shows hypercapnia?

FIGURE 25. Key components of the assessment of acute respiratory failure. A-a = alveolar-arterial; ABG = arterial blood gas.

or supraglottic device or laryngeal mask airway can aid oxygenation and ventilation when immediate intubation is not feasible and may be used until the airway can be secured.

Respiratory failure can result from obstruction or compression of the upper airways. Patients with partial airway obstruction may have tachypnea, stridor, increased respiratory effort, or an upright (tripod) posture with the use of accessory muscles. Absent air movement, inability to talk, or cyanosis suggests complete obstruction, which is a medical emergency. Inspiratory stridor suggests obstruction at or above the vocal cords, whereas expiratory stridor and wheezing suggest an intrathoracic process. Pulse oximetry in the setting of partial upper airway obstruction and stridor is usually normal. In patients with respiratory distress or for whom the risk for respiratory deterioration is high, early intubation is indicated.

KEY POINT

- In patients who cannot maintain a patent airway or protect their airway against aspiration, a secure airway should be established by inserting a cuffed endotracheal or tracheostomy tube.

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is caused by inadequate oxygenation of hemoglobin. The most common cause of hypoxemic respiratory failure is shunt, which is an extreme ventilation/perfusion (V/Q) mismatch (V/Q = 0), which occurs when perfused areas of the lung are not ventilated. There are two main causes: alveolar collapse (atelectasis) and alveolar filling with blood, cells, protein, or water. The key feature of the shunt is an increased alveolar-arterial oxygen gradient not responsive to oxygen supplementation, derived by subtracting the measured arterial $\mathrm{Po_2}$ from the calculated alveolar $\mathrm{Po_2}$ from the alveolar gas equation:

$$\text{Alveolar } \mathrm{Po_2} = (\mathrm{Fio_2} \times [\mathrm{P_{atm}} - 47]) - (1.25 \times \mathrm{Pco_2})$$

$\mathrm{Fio_2}$ is the fraction of inspired oxygen (0.21 in ambient air), $\mathrm{P_{atm}}$ is the atmospheric pressure (760 mm Hg at sea level), and 47 represents the partial pressure of water in mm Hg at 37°C (98.6°F).

Features of acute hypoxemic respiratory failure include recent onset of increased work of breathing, tachypnea, and anxiety. Cyanosis of the lips or fingers may be present when oxygenation of hemoglobin is severely compromised—often below 80%. Auscultation of crackles, wheezing, egophony, or rhonchi may suggest underlying etiologies. Clubbing suggests chronic diseases. Findings on chest imaging may be helpful to identify the cause of acute respiratory failure.

Treatment of hypoxemic respiratory failure includes administration of supplemental oxygen, mechanical ventilation (with positive end-expiratory pressure, or PEEP) to open alveoli, and in severe cases, extracorporeal membrane oxygenation (ECMO). Disease-specific management is discussed here.

KEY POINTS

- The most common cause of hypoxemic respiratory failure in the ICU is shunt, which occurs when perfused areas of the lung are not ventilated, whether because of alveolar collapse (atelectasis) or alveolar filling with blood, protein, or water.
- Management of hypoxemic respiratory failure centers on administration of supplemental oxygen and measures to open alveoli that are fluid-filled or collapsed.

Acute Inhalational Injuries

Pulmonary complications are a leading cause of morbidity and mortality in burn patients or those who experience significant smoke exposure from fires. Direct thermal injury resulting from smoke inhalation is usually limited to the upper airways. However, steam inhalation causes direct thermal injury throughout the tracheobronchial tree because of its ability to carry heat more efficiently than dry, hot gas. After smoke inhalation, one third of patients develop airway edema or mucosal sloughing from epithelial necrosis. Chest physiotherapy and serial bronchoscopy are frequently necessary to facilitate continued airway clearance. Injury to the distal tracheobronchial tree and lung parenchyma is caused by chemicals in smoke that generate a combination of bronchoconstriction, pulmonary edema, V/Q mismatch, and bronchial cast formation. Treatment is supportive.

Secondary infections after inhalational injury are common and are a major cause of morbidity and mortality. Pneumonia is the most common complication after smoke inhalation, especially from *Staphylococcus* and *Pseudomonas* species. Toxicity from carbon monoxide (CO) and hydrogen cyanide (HCN) are common after smoke inhalation and should be suspected in all patients with smoke exposure. Management of these toxicities is discussed in the section on Specific Critical Care Topics.

Inhalational injuries related to chemical vapors are uncommon. War, industry, farming, and exposure to home cleaning or pesticide agents constitute most chemical inhalation injuries. Water-soluble agents usually affect mucosal structures of the upper airway and have rapid onset of symptoms. Water-insoluble agents affect deeper structures including lung parenchyma and distal airways, and symptoms are often delayed. Edema, bronchospasm, asphyxiation, and direct systemic toxicity are common. Key features of inhalational agents are listed in **Table 53**. Treatment is supportive. In patients with cholinesterase inhibitor exposure (typically organophosphate pesticides), high-dose atropine is administered until bronchorrhea and bronchospasm are controlled.

E-cigarette- or vaping-associated lung injury (EVALI) represents another type of inhalational injury. Vitamin E acetate, used to thicken illicit vaping products, is linked to toxicity. Clinical suspicion for EVALI should be high in patients who use e-cigarettes or vaping devices, have hypoxemia, and report respiratory symptoms (cough, dyspnea) or gastrointestinal

TABLE 53. Key Features of Inhaled Agents

Agent	Characteristics	Clinical Features After Exposure
Ammonia	Colorless; ammonia odor	Cough, upper airway burns, pulmonary edema, asphyxiation in poorly vented areas
Chlorine	Yellow-green; chlorine odor	Upper airway irritation and burns, bronchospasm, pulmonary edema
Phosgene	Colorless; musty odor like fresh-cut grass	Systemic toxicity, including elevated methemoglobin level, cyanosis, and metabolic acidosis; pulmonary edema
Mustard gas	Yellow-brown vapor; odor like garlic or onions	Upper airways burns and obstruction can occur
Organophosphates and other cholinesterase inhibitors	Colorless; fruity odor	Systemic toxicity causing acetylcholine toxicity (rhinorrhea, bronchorrhea, diarrhea, bronchospasm, bradycardia, flaccid paralysis, apnea)

symptoms (abdominal pain, vomiting, diarrhea). Patients may also have constitutional symptoms (fever, chills). Reported cases of EVALI have declined sharply since their peak in September 2019. CDC guidelines on diagnosis and treatment of EVALI are available at https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a syndrome characterized by acute hypoxemia and diffuse lung injury as a result of an inciting insult. The most common causes are sepsis and pneumonia, but there are other causes of ARDS (**Table 54**).

In ARDS, disruption of surfactant, vascular endothelial injury, and alveolar epithelial injury lead to fluid and protein extravasation into interstitial and alveolar spaces and alveolar collapse, V/Q mismatch, and decreased lung compliance. Histology shows diffuse alveolar damage (**Figure 26**).

ARDS has no specific diagnostic test. The most recent ARDS diagnostic consensus is summarized in the 2012 Berlin Definition of ARDS (**Table 55**). Patients with ARDS are at high risk for mortality, which increases with ARDS severity. Importantly, mortality is usually the result of underlying disease, secondary infection, or multiorgan dysfunction rather than refractory respiratory failure.

TABLE 54. Common Causes of Acute Respiratory Distress Syndrome

Direct Pulmonary Injury
Aspiration of gastric contents
Fat embolism
Near drowning
Pneumonia (including viral causes such as COVID-19)
Smoke or chemical inhalation
Thoracic trauma/thoracic contusion
Indirect Pulmonary Injury
Disseminated intravascular coagulation
Nonthoracic trauma
Pancreatitis
Pulmonary reperfusion injury (after lung transplantation)
Sepsis/septic shock
Transfusion of blood products

Ventilatory Management

Most patients with ARDS are managed with invasive mechanical ventilation. PEEP and low tidal volume ventilation are the cornerstones of ARDS management, as they are associated with improved patient outcomes. In ARDS, the lung injury is not homogenous—it is characterized by areas of noncompliant lung adjacent to lung with more normal compliance. The compliant lung is susceptible to overdistention and injury by tidal volume (volutrauma). Based on evidence showing an 11% absolute reduction in reduction in mortality, guidelines recommend a tidal volume of 4 to 8 mL/kg of predicted body weight and a plateau pressure less than 30 cm H_2O.

PEEP prevents lung injury associated with repeated opening and closing of distal airways and alveoli (atelectrauma). It improves homogeneity of the lung parenchyma by reducing

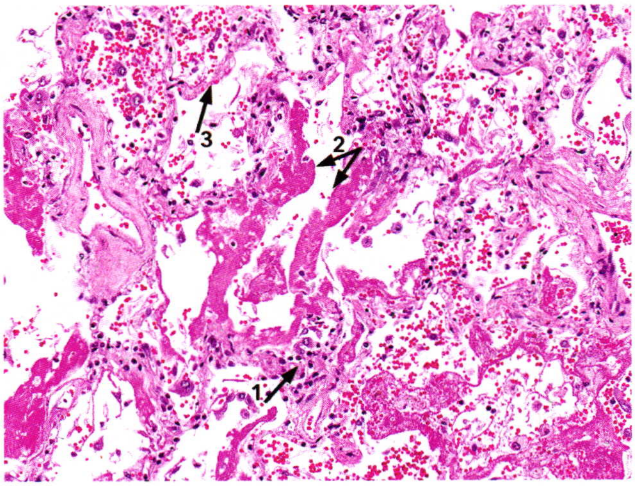


FIGURE 26. Diffuse alveolar damage. 1 = interstitial edema (thickened cellular space between airspace and vasculature); 2 = hyaline membranes (proteinaceous alveolar exudates that accumulate along the alveolar surfaces and impair gas exchange); 3 = denuded epithelium (usually numerous type 1 alveolar cells have undergone apoptosis and been replaced by hyaline membrane or fibrosis).

TABLE 55. 2012 Berlin Definition of Acute Respiratory Distress Syndrome

The following criteria must be met:

- Onset within 1 week of known ARDS insult (most cases occur within 72 hours)
- Bilateral opacities on chest imaging consistent with pulmonary edema
- Respiratory failure not related to cardiac failure or volume overload
- Arterial $\text{Po}_2/\text{Fio}_2 < 300$ on at least 5 cm H_2O PEEP from noninvasive or invasive mechanical ventilator

Once criteria for diagnosis are met, severity of ARDS is based on the following criteria:

- Mild = arterial $\text{Po}_2/\text{Fio}_2 > 200$ to < 300
- Moderate = arterial Po_2/Fio_2 100 to 200
- Severe = arterial $\text{Po}_2/\text{Fio}_2 < 100$

ARDS = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure.

Information from Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526-2533. [PMID: 22797452] doi:10.1001/jama.2012.5669

differences in regional lung compliance and improves V/Q mismatch by maintaining alveolar recruitment. There is no definitive level of optimal PEEP for the ventilation of patients with ARDS. The favored method of selecting PEEP is to use a PEEP-Fio_2 table, where PEEP is matched to the needed Fio_2 to maintain a target saturation of 88% to 95%. Guidelines recommend using higher PEEP in patients with moderate to severe ARDS. However, a recent trial comparing higher PEEP and recruitment maneuvers to a lower PEEP strategy in moderate to severe ARDS showed an increase in mortality with higher PEEP.

Prone positioning reduces compression of portions of the lung behind the cardiac and mediastinal structures and improves V/Q matching in patients with ARDS. A large randomized trial demonstrated improved mortality in patients with an arterial Po_2/Fio_2 ratio less than 150 who were treated with early-onset (less than 48 hours) prone positioning and low tidal volume ventilation. Prone positioning for at least 12 to 16 hours a day should be considered for patients with severe ARDS (Po_2/Fio_2, less than 150; Fio_2, at least 60).

Two large trials have evaluated the role of ECMO in the management of ARDS; both trials demonstrated feasibility and trends toward decreased mortality. At this time, ECMO is part of the therapeutic options for patients with severe refractory respiratory failure resulting from ARDS. Early evaluation is recommended in patients with severe ARDS.

Other methods to optimize ventilator management in ARDS have been suggested, including recruitment maneuvers, inverse ratio ventilation, airway pressure release ventilation, esophageal pressure, and driving pressure-guided titration of PEEP, as well as high-frequency oscillatory ventilation. None of these methods has demonstrated a mortality benefit in ARDS.

KEY POINT

- Treating patients with severe acute respiratory distress syndrome using early prone positioning and low tidal volume ventilation has demonstrated clinically important mortality benefit.

Nonventilatory Management

Although mortality in ARDS has decreased, the morbidity associated with ARDS is recognized as a major factor in survivors' well-being. Many interventions will have lasting effects beyond hospital discharge. Sedation and analgesia guidelines (discussed in the Principles of Critical Care section) are designed to limit the complications of sedative and opioid medications.

Volume overload is recognized as a source of morbidity. The Fluids and Catheters Treatment Trial compared conservative with liberal fluid strategies in patients with ARDS. Although mortality did not differ between groups, patients who were treated with conservative fluid management showed improved oxygenation and decreased time on the ventilator and in the ICU. Patients who are hemodynamically stable and do not have end-organ hypoperfusion should receive protocol-directed diuretics and management to minimize fluid administration.

Paralytic agents in ARDS are used to increase oxygenation and decrease ventilator-induced lung injury. Although initial trials indicated a mortality benefit, the more recent Reevaluation of Systemic Early Neuromuscular Blockade trial showed that among patients with moderate to severe ARDS who were treated with a strategy of high PEEP, there was no significant difference in 90-day mortality between patients who receiving cisatracurium infusion and those treated with lighter sedation targets. There was a non–statistically significant increase in subsequent ICU-acquired weakness in paralyzed patients.

Sedation strategies have an effect on outcomes. The current recommendation is to lighten sedation as soon as it is safe, to allow patient interaction. A multicenter, randomized trial among ventilated ICU patients showed no difference in 90-day mortality between those assigned to no sedation and those assigned to light sedation with daily interruption. The study highlighted the importance of daily awakening, reassessment of the sedation strategies, and minimizing mind-altering medications.

Other therapies, including nutritional modifications, glucocorticoid administration, vitamin C, macrolide antibiotics, inhaled nitric oxide, prostacyclin analogues, and stem cells or granulocyte-macrophage colony-stimulating factor, have conflicting or limited evidence and are not recommended in the management of ARDS.

Heart Failure

Acute cardiogenic pulmonary edema often presents with hypoxemic respiratory failure. In patients who present with acute respiratory failure, but no clear trigger for ARDS, it is important to evaluate for cardiogenic causes, which include cardiomyopathy, mitral and aortic valve disease, myocardial ischemia, and arrhythmias (particularly atrial fibrillation with rapid ventricular rate). Evaluation for a cardiac cause of pulmonary edema should include an assessment for volume overload (jugular venous distention, S_3, peripheral edema), an electrocardiogram, B-type natriuretic peptide, serial serum troponins, and an echocardiogram.

In general, acute cardiogenic pulmonary edema responds promptly to therapy with diuretics and afterload reduction (vasodilators or inodilators). Systematic reviews demonstrate that noninvasive positive pressure ventilation (continuous positive airway pressure or bilevel positive airway pressure) hastens the resolution of hypoxemia, improves symptoms, lowers intubation rates, and decreases mortality compared with oxygen therapy alone.

KEY POINT

- In cardiogenic pulmonary edema, noninvasive positive pressure ventilation (continuous positive airway pressure or bilevel positive airway pressure) hastens the resolution of hypoxemia, improves symptoms, lowers intubation rates, and decreases mortality compared with oxygen therapy alone.

Atelectasis

Atelectasis is a common postoperative complication. Pain or impaired respiratory mechanics after thoracic and abdominal surgeries can lead patients to adopt shallow breathing patterns and to avoid coughing. Patients may be asymptomatic or present with diminished breath sounds at the lung bases, consolidation on imaging, egophony, rhonchi, and labored breathing. Management includes pain control, encouraging mobility, and secretion management. Respiratory physiotherapy (inspiratory muscle training, deep breathing exercise, mobility programs, or percussion and vibration therapy) help prevent atelectasis. Bronchoscopy for routine airway mucous clearance offers no clear benefit compared with other methods of chest physiotherapy. It should be considered whether 24 hours of chest physiotherapy fails to decrease the atelectasis. If secretions are minimal, positive pressure airway therapy (positive expiratory pressure devices) to recruit collapsed alveoli may be considered. No evidence exists for use of mucolytics such as N-acetyl cysteine for treatment of atelectasis.

KEY POINT

HVC

- Strategies to prevent postoperative atelectasis include pain control, early mobility, and secretion management with aggressive chest physiotherapy; bronchoscopy for airway mucous clearance offers no clear benefit compared with other methods of chest physiotherapy.

Pneumonia

Pneumonia is a common cause of respiratory failure in the ICU and is the most common cause of ARDS that develops outside the hospital. In patients with an appropriate history, chest radiograph is the standard for diagnosis. However, a negative clinical examination or chest radiograph does not necessarily rule out community-acquired pneumonia in symptomatic patients, especially in older adults. Therefore, the absence of typical features or focal infiltrates on chest radiograph should not preclude early antibiotic administration to persons with an otherwise high probability of pneumonia. For further discussion of community-acquired pneumonia, see MKSAP 19 Infectious Disease. In patients who do not respond appropriately to antibiotics, repeat sputum cultures should be obtained and nonbacterial causes of infection and noninfectious causes should be considered. In addition, further evaluation with chest ultrasonography, chest CT, or bronchoscopy should be considered to evaluate for complicating factors such as pleural effusion, abscess, or airway obstruction stemming from malignancy or foreign body aspiration.

KEY POINT

- A negative clinical examination or chest radiograph does not necessarily rule out community-acquired pneumonia in symptomatic patients, especially in elderly individuals.

Diffuse Parenchymal Lung Disease

Acute exacerbations of diffuse parenchymal lung disease, particularly idiopathic pulmonary fibrosis, can occur either as a complication of an inciting event (infection, postprocedural, drug reaction) or, in many cases, for unknown reasons. The criteria for identifying acute exacerbations include previous or concurrent diagnosis of diffuse parenchymal lung disease, acute worsening of respiratory status (less than 1 month), and new ground-glass opacities on imaging studies. The mortality in patients with hypoxemic respiratory failure resulting from an exacerbation of idiopathic pulmonary fibrosis exceeds 50%. Most patients with hypoxemic respiratory failure caused by idiopathic pulmonary fibrosis are treated empirically with antibiotics and high-dose glucocorticoids or other immunosuppressants, but the data are insufficient to recommend specific doses, duration, or certainty of benefit. Outcomes after intubation and mechanical ventilation are very poor, as mortality can approach 100%. Therefore, many clinicians recommend that goals-of-care discussions be held and palliative care strategies be determined early in the clinical course and that other therapies, such as ECMO, only be offered as a bridge for patients eligible for (and already listed for) lung transplantation. See Diffuse Parenchymal Lung Disease section.

KEY POINT

- Because outcomes after intubation and mechanical ventilation are very poor for patients with acute exacerbations of idiopathic pulmonary fibrosis, goals of care and palliative care strategies should be discussed early and other therapies, such as extracorporeal membrane oxygenation, should only be offered as a bridge for patients eligible for lung transplantation.

Pulmonary Embolism

Pulmonary embolism (PE) causes respiratory failure primarily through V/Q mismatch. After an acute PE, resistance to pulmonary blood flow increases both because of thrombosis and because of the vasospasm of adjacent pulmonary blood vessels from inflammatory mediators. Blood flow is directed to other areas of normal lung, which become overperfused. If alveolar oxygen levels in the normal lung are insufficient to fully oxygenate blood in the overperfused vessels, hypoxemia ensues. Chest radiograph or chest CT scan may demonstrate peripheral, ground-glass, wedge-shaped opacities (Hampton hump sign) signifying the presence of infarcted lung and surrounding atelectasis. Blood flow through atelectatic lung can result in shunt and worsened hypoxemia.

Pulmonary emboli can also cause strain on the right ventricle (RV) if the PE causes significant pulmonary arterial obstruction. Cardiac output may be impaired, leading to reduced mixed venous oxygen saturation, especially when metabolic demands exceed cardiac capacity. If this occurs in conjunction with V/Q mismatch and shunt, blood cannot fully saturate with oxygen before leaving the alveolar capillaries. This adds to hypoxemia and subsequent respiratory failure.

Although most patients with hypoxemia after PE can be managed with supplemental oxygen alone, some patients require intubation and mechanical ventilation. Mechanical ventilation produces several physiologic effects that need to be considered in the patient with PE and RV dysfunction. Increased intrathoracic pressures from mechanical ventilation can decrease venous return and RV preload. Increased alveolar pressures can compress capillaries and increase RV afterload. These effects can lead to further RV dysfunction and hemodynamic instability. Although there is no absolute contraindication to mechanical ventilation in patients with underlying PE, the possibility of rapid hemodynamic instability must be anticipated. This is usually managed with vasopressors (norepinephrine), oxygen, careful use of PEEP, and sometimes pulmonary vasodilators (inhaled nitric oxide or epoprostenol). In patients with hemodynamic collapse, treatment with thrombolytics is associated with decreased mortality and improved clinical and echocardiographic parameters.

Thrombolytic therapy has up to a 2% risk of intracranial hemorrhage, and this should be considered relative to the risk for massive PE leading to hemodynamic collapse. In patients with contraindications to thrombolysis, or in those in whom thrombolysis has failed, surgical or percutaneous catheter-based embolectomy is an option if resources are available. For further discussion of PE, see MKSAP 19 Hematology.

Hypercapnic (Ventilatory) Respiratory Failure

Hypercapnic, or ventilatory, respiratory failure occurs when alveolar ventilation is inadequate to clear the CO_2 produced by cellular metabolism and the level of CO_2 increases in the blood. Hypercapnia reflects alveolar hypoventilation, an increased metabolic load that is not matched by an increase in alveolar ventilation, or both. Alveolar hypoventilation occurs when the patient is unable to ventilate because of decreased respiratory drive, decreased tidal volume (V_T), or increased volume of dead space (V_D) relative to the overall tidal volume (V_D/V_T) (**Table 56**).

TABLE 56. Causes of Acute Hypercapnic Respiratory Failure

Decreased Respiratory Drive
Anesthesia
Central apnea
Obesity hypoventilation syndrome
Drugs (e.g., opioids, benzodiazepines, ethanol)
Encephalitis
Hypothermia
Hypothyroidism
Meningitis
Stroke
Decreased V_T or Increased V_D/V_T
Neuromuscular weakness
Amyotrophic lateral sclerosis
Botulism
Critical illness myopathy
Guillain-Barré syndrome
Myasthenia gravis
Myositis (polymyositis, dermatomycosis)
Polio
Spinal or phrenic nerve injury
Metabolic
Electrolyte disorder (low magnesium, low phosphate)
Obstructive airway disease
Asthma exacerbation
Bronchiectasis flare (including cystic fibrosis)
COPD exacerbation
Restrictive physiology
Ankylosing spondylitis
Multiple rib fractures (flail chest)
Thoracic cage deformity (kyphoscoliosis)

V_D = volume of dead space; V_T = tidal volume.

Clinical features of acute hypercapnic respiratory failure are variable and nonspecific. Symptoms may include somnolence and myoclonic jerks in the setting of CO_2 narcosis. In some cases, increased work of breathing may precede the development of acute hypercapnic respiratory failure. Underlying chest wall deformity, neurologic weakness, or polycythemia should also prompt evaluation for hypercapnia in the setting of respiratory failure.

Patients presenting with hypercapnic respiratory failure frequently have coexisting hypoxemia. In these cases,

TABLE 57. Features of Acute and Chronic Hypercapnia

Laboratory Study	Acute Hypercapnia	Chronic Hypercapnia
pH	<7.35	~7.35-7.40
Arterial P_{CO_2}	>45 mm Hg (6.0 kPa)	>45 mm Hg (6.0 kPa)
Bicarbonate concentration $[HCO_3]$	22-26 mEq/L (22-26 mmol/L)	>26 mEq/L (26 mmol/L)
Expected metabolic compensation	1.0 mEq/L ↑ (1 mmol/L) $[HCO_3]$ for each 10 mm Hg (1.3 kPa) ↑ in arterial P_{CO_2}	3.5 mEq/L (3.5 mmol/L) ↑ $[HCO_3]$ for each 10 mm Hg (1.3 kPa) ↑ arterial P_{CO_2}

administration of supplemental oxygen may decrease hypoxemia, but it may increase hypercapnia (mechanisms include V/Q mismatch, decreased respiratory drive, and the Haldane effect). This is particularly dangerous for patients with neuromuscular diseases, as they may rapidly become more hypercapnic, leading to obtundation and respiratory arrest. All patients who are suspected of acute hypercapnic respiratory failure should have arterial blood gas analysis even if hypoxemia resolves with oxygen administration (**Table 57**). The pH helps to determine the acuity and severity of respiratory failure. In chronic hypercapnia, pH changes are less marked because of metabolic compensation resulting in increased serum bicarbonate levels. See MKSAP 19 Nephrology for further discussion of respiratory acidosis.

Management of an elevated arterial P_{CO_2} depends on the clinical situation and the resultant pH. For instance, an elevated arterial P_{CO_2} may represent the baseline in patients with COPD; however, in patients with asthma, the development of elevated arterial P_{CO_2} may indicate imminent respiratory failure requiring emergent intubation.

KEY POINT

- All patients who are suspected of acute hypercapnic respiratory failure should have arterial blood gas analysis even if hypoxemia resolves with oxygen administration.

Decreased Respiratory Drive

Decreased respiratory drive leads to diminished alveolar CO_2 clearance and hypercapnia. Patients often present with somnolence and difficulty protecting their airway. Noninvasive positive pressure ventilation (NPPV) should be considered for patients who can protect their airway. This improves minute ventilation and gas exchange. If airway protection is compromised or there is either significant respiratory acidosis (pH less than 7.25) or hemodynamic instability, intubation and mechanical ventilation are indicated.

Drug Overdose

Sedating drugs (illicit or prescribed), anesthetics, and severe alcohol intoxication can lead to depressed central respiratory drive. In addition to management as outlined earlier, contact with a local poison control center is helpful to determine the most appropriate care of the patient. See discussion of specific agents in the Specific Critical Care Topics section.

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome is characterized by the presence of obesity, sleep-disordered breathing, and persistent daytime hypercapnia (arterial P_{CO_2} greater than 45 mm Hg [5.9 kPa]). Hypercapnia stems from low tidal volumes and inappropriate central respiratory response. Acute hypercapnic respiratory failure attributable to obesity hypoventilation syndrome should be a diagnosis of exclusion. The 2019 guidelines from the American Thoracic Society recommend that hospitalized patients suspected of having this syndrome be started on noninvasive ventilation with either bilevel positive airway pressure or volume-targeted pressure support and continued on this therapy until they undergo outpatient evaluation for obstructive sleep apnea.

Arterial blood gases should be monitored within 2 hours of initiation of NPPV to ensure clinical improvement. If patients do not improve with adequate NPPV, intubation is warranted. Respiratory stimulants such as acetazolamide, theophylline, or a progestin have theoretical benefit to patients, but limited data supporting their use in this setting.

KEY POINTS

- Obesity hypoventilation syndrome is characterized by the presence of obesity, sleep-disordered breathing, and persistent daytime hypercapnia (arterial P_{CO_2} greater than 45 mm Hg [5.9 kPa]).
- Noninvasive ventilation with bilevel positive airway pressure or volume-targeted pressure support is the key to improving hypercapnia in hospitalized patients with obesity hypoventilation syndrome.

Decreased Tidal Volume and Increased Dead Space

Neuromuscular Weakness

The diaphragm is the main muscle responsible for inspiration and accounts for more than two thirds of the ventilatory work. The C3-C5 cervical nerve roots form the phrenic nerves, which directly innervate the diaphragm. Diaphragmatic weakness is common in the ICU. Common causes are postsurgical phrenic nerve injury and ICU-acquired weakness.

Patients with diaphragmatic weakness develop orthopnea, shallow breathing, and paradoxical movement of the chest wall and abdomen. Intercostal and abdominal wall muscles are required for coughing. Lower cervical and upper thoracic nerve roots supply the intercostal and abdominal wall muscles. Weak cough, difficulty managing secretions, or a change in voice may point to bulbar weakness.

Assessment of cranial nerves and respiratory muscle function is important in a patient with suspected neurologic disease. Specific components of pulmonary function testing can be helpful but are effort-dependent (**Table 58**). Facial,

TABLE 58. Pulmonary Function Values Suggestive of Neuromuscular Weakness

Function	Value
FVC	>20% decrement in FVC while supine compared with upright position
Maximal inspiratory pressure	Less than −60 cm H_2O or 50% of predicted
Maximal expiratory pressure	Less than +60 cm H_2O or 50% of predicted

bulbar, or postural weakness can affect accurate measurement. Pressure measurements may be falsely low in patients with severe obstructive lung disease

Guillain-Barré syndrome and myasthenic crisis are the most common causes of acute neurologic respiratory failure in the ICU. Patients with Guillain-Barré syndrome generally present with ascending symmetric paralysis and areflexia occurring during the course of 2 to 4 weeks. Dysautonomia is common and can cause hemodynamic instability or cardiac arrhythmias. In myasthenic crisis, the hallmark feature is muscle fatigability. Diplopia, ptosis, dysarthria, limb weakness, and weak cough are common. See MKSAP 19 Neurology for further discussion of Guillain-Barré syndrome and myasthenic crisis.

In the 25% of patients with Guillain-Barré syndrome who develop respiratory failure, intubation is necessary because respiratory function can take days to weeks to recover. In myasthenic crisis, early NPPV may prevent the need for intubation; the ability to protect the airway and to cough must be carefully evaluated in such patients.

Acute spinal cord injuries at or above the C5 level invariably require mechanical ventilation. In some cases (complete spinal cord injury below C3 or incomplete injury above C3), recovery of independent respiratory function can occur. However, atelectasis, aspiration pneumonia, and pulmonary emboli are common and can lead to recurrent acute hypercapnic respiratory failure. NPPV and mechanical cough assist devices are essential in the management and prevention of these events.

KEY POINTS

- Guillain-Barré syndrome and myasthenic crisis are the most common causes of acute neurologic respiratory failure in the ICU.
- Evaluation of maximum inspiratory and expiratory pressures and positional changes in vital capacity are helpful in assessing neuromuscular weakness as a cause of hypercapnic respiratory failure.

Restrictive Chest Wall Disease

Restrictive disease from disorders affecting the pulmonary parenchyma (such as diffuse parenchymal lung disease) primarily leads to hypoxemia without hypercapnia. Acute hypercapnic respiratory failure is more common in patients with extrapulmonary chest wall restriction (pectus deformity, scoliosis, kyphosis), which causes compromised respiratory mechanics. Ascites and severe bowel distention can also compromise respiratory mechanics by exerting a significant cephalad force on the diaphragm. Extrapulmonary chest wall restriction usually causes poor ventilatory reserve without overt respiratory failure. However, acute insults such as infection or sedating medications can precipitate hypercapnic respiratory failure. NPPV or invasive mechanical ventilation may be appropriate while the precipitating condition is managed. In patients with thoracic cage deformity, NPPV is frequently sufficient.

Obstructive Lung Diseases (Asthma and COPD)

The physiologic hallmark of obstructive lung diseases is hyperinflation. The main driver is high airway resistance resulting from structural changes, inflammation, high cholinergic tone, and mucous plugging. When combined with a decrease in the lung's elastic recoil (as observed in emphysema), this results in increased total lung capacity and functional residual capacity (lung volume at end exhalation).

The degree of airflow obstruction and the respiration rate both contribute to dynamic hyperinflation. Because of high airflow resistance, air in the lungs does not have enough time to exit before the next breath begins, which increases the functional residual capacity and limits the inspiratory capacity. When the intrathoracic pressure remains positive at the end of exhalation because of this trapped volume, it is called auto-PEEP. Dynamic hyperinflation, auto-PEEP, and decreased elastic recoil of the lung all contribute to disordered lung mechanics, increased work of breathing, and respiratory muscle fatigue. When patients are on mechanical ventilation, auto-PEEP may decrease venous return and contribute to hemodynamic instability. The main strategies to minimize auto-PEEP are to prolong the expiratory time (with lower respiration rate) and administer bronchodilators.

At the time of a COPD exacerbation, patients may present with signs of increased respiratory work. They may also have findings related to the presence of hypercapnia, such as somnolence. See Airways Disease section for more detailed information about the management of COPD exacerbations.

In patients with COPD, excessive oxygen can worsen hypercapnia by three mechanisms: increasing V/Q mismatch, decreasing respiratory drive, and the Haldane effect. Oxygen therapy should be titrated to 88% to 92% SpO_2. In patients with hypercapnic respiratory failure resulting from COPD exacerbation, NPPV is preferred as the initial means to reduce P_{CO_2}; bilevel positive airway pressure is the most commonly used and most effective NPPV mode for this condition. If patients cannot protect their airway, are hemodynamically unstable, or do not improve on NPPV, intubation and mechanical ventilation are necessary.

In patients with asthma, upright posture, inability to speak in full sentences, diaphoresis, flaring of the nares, and use of accessory muscles during inspiration are signs of impending respiratory failure. Blood gases usually demonstrate respiratory alkalosis resulting from rapid, shallow breathing patterns, but when the P_{CO_2} becomes normal or elevated, it may signal impending respiratory failure. Oxygen should be given to maintain a hemoglobin saturation of 90% to 95%.

In cases of severe asthma exacerbation refractory to conventional management, therapies with lower levels of evidence, such as magnesium sulfate or heliox, may be used. Other adjunctive therapies are not recommended because of lack of demonstrated efficacy. Antibiotics should not be administered unless there is evidence of infection.

Little evidence supports the use of NPPV in asthma exacerbations. If used, close monitoring is required. For most patients with asthma with respiratory failure, mechanical ventilation and intubation are recommended. As with COPD, efforts should be directed at maximizing expiratory time, as this reduces auto-PEEP. Doing so often requires sedation or paralytics and can lower the overall minute ventilation. Because this may increase arterial P_{CO_2}, arterial blood gas analysis should be performed frequently in these patients. See Airways Disease section for more detailed information about management of asthma exacerbations.

KEY POINTS

- Patients with hypercapnic respiratory failure and COPD exacerbation benefit from noninvasive positive pressure ventilation, provided they can protect their airway and are hemodynamically stable.
- In patients with asthma with respiratory failure, intubation and mechanical evaluation are recommended rather than noninvasive positive pressure ventilation.
- **HVC** In severe refractory asthma, anesthetics with bronchodilator properties (aminophylline, mucolytics, and leukotriene receptor antagonists) are not recommended.

Shock

Shock occurs when systemic tissue perfusion is inadequate. In early states of tissue hypoperfusion, aerobic metabolism is supplanted by anaerobic metabolism and tissue injury is reversible. As compensatory mechanisms fail, sustained organ hypoperfusion can lead to cellular dysfunction and death. There are four primary mechanisms of shock: decreased circulating volume (hypovolemic), pump failure (cardiogenic), circulatory obstruction (obstructive), and inappropriate vasodilation (distributive)—these mechanisms may overlap.

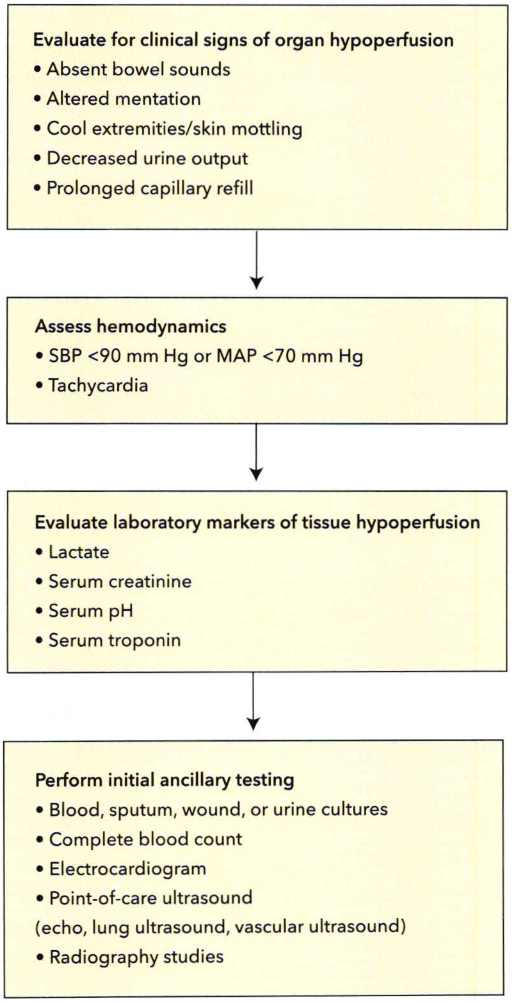
Hypotension alone should not be considered diagnostic of end-organ hypoperfusion. Instead, blood pressure should be considered in the context of other physical examination findings that may suggest end-organ hypoperfusion (**Table 59**).

TABLE 59. Common Clinical Findings in Patients With Shock

Altered mentation
Capillary refill time (>2 s)
Elevated serum lactate (>3 mEq/L [3 mmol/L])
Hypotension (SBP <90 mm Hg) or >30 mm Hg drop in SBP from baseline
Mottled skin
Tachycardia (heart rate >100/min)
Tachypnea (respiration rate >20/min)
Urine output <0.5 mL/kg/h

SBP = systolic blood pressure.

A thorough examination of the patient, laboratory results, and ancillary studies (**Figure 27**) are essential to identifying the type of shock present (**Table 60**). The use of point-of-care ultrasound to aid in shock assessment is increasing. Echocardiography can provide useful data regarding cardiac function and cardiac response to treatment. Vascular, lung, and abdominal ultrasonography improve procedural safety and can rapidly assess for venous thrombosis and pleural or abdominal abnormalities. Evidence for pulmonary artery catheters demonstrates a lack of benefit and, in some cases, increased risk to patients. Despite this, pulmonary artery catheters may provide diagnostic utility in select patients who require assessment of cardiopulmonary pressures or cardiac output, such as those with pulmonary



Evaluate for clinical signs of organ hypoperfusion
- Absent bowel sounds
- Altered mentation
- Cool extremities/skin mottling
- Decreased urine output
- Prolonged capillary refill

Assess hemodynamics
- SBP <90 mm Hg or MAP <70 mm Hg
- Tachycardia

Evaluate laboratory markers of tissue hypoperfusion
- Lactate
- Serum creatinine
- Serum pH
- Serum troponin

Perform initial ancillary testing
- Blood, sputum, wound, or urine cultures
- Complete blood count
- Electrocardiogram
- Point-of-care ultrasound
(echo, lung ultrasound, vascular ultrasound)
- Radiography studies

FIGURE 27. Evaluation of shock. MAP = mean arterial pressure; SBP = systolic blood pressure.

TABLE 60. Selected Causes of Shock

Distributive
Anaphylaxis
Drugs (peripheral vasodilators, nitrates)
Sepsis
Spinal injury (usually above T4 level)
Hypovolemic
Acute blood loss (trauma, GI bleeding, surgery, uterine bleeding, obstetrical, retroperitoneal bleeding, aortic rupture)
Crush injury, rhabdomyolysis
Cutaneous losses (burns, toxic epidermal necrolysis, erythroderma, excessive sweating)
Drugs (diuretics, laxatives)
GI losses (vomiting/diarrhea)
Kidney losses (diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, adrenal insufficiency, post-ATN osmotic diuresis)
Cardiogenic
Arrhythmia (tachycardia, bradycardia)
Heart failure
Pulmonary hypertension
Myocardial infarction
Valvular heart disease (critical stenosis, severe insufficiency, valve perforation, papillary muscle or chordae rupture)
Ventricular septal rupture
Obstructive
Abdominal compartment syndrome
Atrial myxoma
Constrictive pericarditis
Pericardial tamponade
Pulmonary embolism
Severe dynamic hyperinflation (e.g., excessive PEEP)
Tension pneumothorax

ATN = acute tubular necrosis; GI = gastrointestinal; PEEP = positive end-expiratory pressure.

hypertension, tamponade, or pericarditis. Other tools that predict response to volume replacement, such as pulse contour analysis, pulse pressure, or stroke volume, variation can also be considered. However, these methods are invasive and carry procedural limitations that may make them impractical or unreliable. Treatment is directed toward correcting the root cause of the shock state.

KEY POINTS

- Treatment of a patient in shock is predicated on distinguishing the type of shock present and directed toward the root cause of the shock state.

HVC
- Evidence for pulmonary artery catheters demonstrates a lack of benefit and, in some cases, increased risk to patients.

Distributive Shock

In distributive shock, the blood volume is generally normal, but a state of "relative" hypovolemia occurs from excessive vasodilation and microvascular dysfunction. Cardiac output is often increased but still cannot maintain a pressure sufficient for normal tissue perfusion. Sepsis is the most common cause of distributive shock, but other disease states present similarly (see Table 60). Initial treatment of distributive shock should focus on fluid resuscitation. Several studies have compared the effectiveness of crystalloid versus colloid administration, with no clear evidence that one is better than the other. A large randomized controlled trial suggested that critically ill patients who were resuscitated using balanced crystalloid solution had a lower composite outcome of death, need for renal replacement therapy, or persistent kidney dysfunction compared with patients receiving normal saline solution. Balanced crystalloid solutions have an electrolyte composition similar to plasma with the addition of a buffer, such as lactate (for example, lactated Ringer solution). If fluid administration alone is insufficient to support tissue perfusion, vasopressor support is warranted. The selection of a vasopressor should be based on the patient's comorbidities and underlying cause of shock.

KEY POINT

HVC
- Several studies have compared the effectiveness of crystalloid versus colloid administration for treatment of distributive shock, with no clear evidence of either's superiority; given the relative expense of colloids, crystalloid administration is generally preferred and recommended by guidelines.

Hypovolemic Shock

Hypovolemic shock occurs when decreased intravascular blood volume causes decreased preload, decreased ventricular filling, and diminished stroke volume. Initially, tachycardia and peripheral vasoconstriction help to preserve perfusion of vital organs but cannot compensate in the setting of severe hypovolemia. Treatment of hypovolemic shock includes aggressive volume or blood product replacement and controlling any source of bleeding. Patients with hemorrhage initially receive intravenous fluids to maintain hemodynamic stability, but ultimately may need erythrocyte transfusion to prevent tissue ischemia. In stable ICU patients, hemoglobin levels should be maintained above 7 g/dL (70 g/L); however, different thresholds and hemoglobin levels may trigger transfusion in actively bleeding patients who are in shock. Higher hemoglobin values may be desirable in patients with underlying cardiovascular disease. In patients with severe trauma resulting in massive blood replacement requirements and coagulopathy, evidence supports early resuscitation with a 1:1:1 ratio of erythrocytes, platelets, and fresh frozen plasma.

Cardiogenic Shock

Arrhythmias, myocardial dysfunction, and valvular disease can lead to decreased cardiac output and cardiogenic shock.

The most common cause of cardiogenic shock is myocardial infarction. Cardiogenic shock-induced tachycardia and vasoconstriction increase afterload and myocardial oxygen demand, often precipitating a further decrease in cardiac output. Initial evaluation should include a focused physical examination, laboratory testing for myocardial ischemia and heart failure, chest radiograph, electrocardiogram, and transthoracic echocardiogram. External or transvenous pacing may be indicated in patients with bradyarrhythmias. Emergent percutaneous intervention or fibrinolytic therapy is indicated if ECG suggests ST-elevation myocardial infarction and laboratory examination supports coronary ischemia. Although not clearly supported by evidence, patients with severe cardiogenic shock may benefit from adjunctive measures as a bridge toward definitive therapy. These include ECMO, intraaortic balloon pumps, and left or right ventricular assist devices. In some cases, these devices can be employed as destination therapy.

Obstructive Shock

Obstructive shock is caused by extracardiac forces that, despite normal cardiac function, act to impair cardiac output. Examples include tamponade, tension pneumothorax, and acute PE. Although hemodynamics frequently mimic those of cardiogenic shock, the clinical presentation of obstructive shock varies depending on the cause. A patient with PE may have signs of elevated right atrial pressure, including jugular venous distention and lower extremity edema, but can have a clear pulmonary exam. A patient with tamponade may have jugular venous distension, pulsus paradoxus, and distant heart sounds. A patient with tension pneumothorax may have absent lung sounds on the affected side of the chest. History and clinical examination should guide ancillary testing and management. Point-of-care lung ultrasound can help rapidly assess patients for pneumothorax, and echocardiography can quickly identify features consistent with PE or pericardial effusion. In some cases, such as constrictive or restrictive pericarditis or pulmonary arterial hypertension, invasive hemodynamic evaluation of cardiopulmonary pressures helps to confirm a diagnosis. Most cases of obstructive shock can be rapidly reversed if promptly identified.

Sepsis

Definition, Pathophysiology, and Clinical Presentation of Sepsis

The Third International Definitions for Sepsis and Septic Shock (Sepsis-3) define sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk for mortality than with sepsis alone.

Infections giving rise to sepsis can include any pathogen and involve any organ. Infections need not be disseminated. The pathophysiology of sepsis is complex and involves dysfunction at many levels, from subcellular mitochondrial dysfunction to failure of entire organ systems. Loss of regulation of the body's finely balanced proinflammatory and antiinflammatory mediators and unregulated coagulation in the microvasculature are characteristic of the syndrome.

Operationally, sepsis can be identified whenever infection is known or suspected and clinical criteria defining organ dysfunction are met. The recommended criteria to assess organ dysfunction are included in the Sequential Organ Failure Assessment (SOFA) score, which assigns a value of 0 to 4 for each of six organ systems assessed: respiratory, coagulation, hepatic, cardiovascular, central nervous, and renal, with increasing scores for more severe dysfunction (online SOFA score calculators are available online: http://clincalc.com/IcuMortality/SOFA.aspx; https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score). An initial SOFA score of 2 or greater or an increase in SOFA score of 2 or more correlates with acute organ dysfunction and predicts hospital mortality of greater than 10%. The SOFA score should be used to assess patients in the ICU.

Sepsis-3 guidelines recommend the use of the simplified quick SOFA (qSOFA) score, a clinical scoring system that includes only three criteria: elevated respiration rate, altered mentation, and hypotension (**Table 61**). A qSOFA score of 2 or greater in the setting of known or suspected infection predicts increased mortality and should prompt evaluation for resuscitation and consideration of ICU admission. Failure to meet two or more qSOFA criteria should not be construed as ruling out sepsis or the need for ICU admission. Recently, the use of qSOFA to predict sepsis has come under increased scrutiny, given conflicting studies regarding its accuracy across different patient populations. Other scoring systems, such as the National Early Warning Score, may outperform qSOFA in predicting in-hospital death and need for ICU admission. Because there is no perfect test for identifying sepsis, scoring systems should not be used as the sole indicator of disease or triage needs.

The criteria for diagnosing septic shock includes hypotension requiring vasopressors to maintain a mean arterial pressure of greater than 65 mm Hg and serum lactate level of greater than 2 mEq/L (2 mmol/L) despite adequate fluid

TABLE 61. qSOFA Score

Criterion	Value	qSOFA Points
Respiration rate	>22/min	1
Systolic blood pressure	<100 mm Hg	1
Mental status	Altered from baseline	1
qSOFA Score	**Predicted Mortality**	
0	<1%	
1	2%-3%	
≥2	≥10%	

qSOFA = quick Sequential Organ Failure Assessment.

resuscitation. Patients who meet these criteria have a 40% or greater risk for in-hospital mortality.

KEY POINT

- The criteria for diagnosing septic shock includes a serum lactate level of greater than 2 mEq/L (2 mmol/L) despite adequate fluid resuscitation and hypotension requiring vasopressors to maintain a mean arterial pressure of greater than 65 mm Hg.

Epidemiology of Sepsis

The epidemiology of sepsis is difficult to judge accurately because of its evolving definition, challenges with clinical recognition of the syndrome, and lack of standardized reporting. However, estimating its clinical and economic effects is possible. There are disparities in sepsis rates among different demographic groups. For example, sepsis is more common among Black men than other racial groups or women. Sepsis is also more common among older adults, with incidence increasing with each year after the age of 65 years. Mortality from sepsis is high. A patient who is septic has a mortality rate 4 or more times greater than for the same underlying condition and comorbidities without sepsis. Mortality increases by roughly 15% for each sepsis-related organ system failure.

Management of Sepsis

For years, sepsis guidelines have focused on early diagnosis and timely treatment of sepsis to improve survival. Early guidelines supported time-based metrics to be achieved in the form of a sepsis "bundle." In 2016 a 3-hour and a 6-hour bundle were proposed on the basis of evidence that bundle-based care led to significant improvements in sepsis mortality. However, subsequent data suggested that in-hospital mortality might be further improved by expediting care within the initial 3-hour window. In 2018 the Surviving Sepsis Campaign issued updated guidelines that combined the previous 3- and 6-hour bundles into a single 1-hour sepsis bundle. The 1-hour bundle includes collection of blood cultures, measurement of serum lactate levels, administration of broad spectrum antibiotics, and provision of fluid or vasopressor resuscitation in patients with hypotension or signs of hypoperfusion. Weak evidence behind some elements of the 1-hour bundle recommendations has generated considerable controversy, but the intent of these recommendations clearly addresses the two main pillars of sepsis management: supporting organ perfusion and controlling the infection.

KEY POINT

- The two main pillars of sepsis management are supporting organ perfusion and function and controlling the infection.

Initial Resuscitation

Sepsis can have serious hemodynamics effects, with decreased preload (resulting from capillary leak), impaired cardiac contractility, and decreased vascular tone. Patients may present in shock, sometimes with profound hypotension requiring large-volume resuscitation with intravenous fluids or vasopressor therapy.

The Surviving Sepsis Campaign guidelines recommend early and aggressive fluid resuscitation. In patients with suspected sepsis, an initial bolus of 30 mL/kg of crystalloid fluid should be given in the first hour of presentation when hypotension or a lactate of at least 4 mmol/L is present. When lactate levels are elevated more than 2 mmol/L, they should be rechecked within 2 to 4 hours to ensure improvement. Although experts agree that aggressive fluid resuscitation is essential, the adequacy of initial fluid resuscitation and the need for further fluid or vasopressors requires clinical judgment based on patient comorbidities and the available data.

When hypotension or hypoperfusion persists, additional fluids or vasopressors may be needed. The Surviving Sepsis Campaign guidelines support using norepinephrine as first-line therapy in patients who require vasopressor support, as it increases systemic vascular resistance without compromising myocardial performance (stroke volume or cardiac output). In cases where norepinephrine alone is insufficient, secondary agents, including epinephrine, vasopressin, or dobutamine, may be considered. Dopamine is not recommended for use in septic shock except in select patients with clinically significant bradycardia, given its association with increased tachyarrhythmia and death compared with norepinephrine. Phenylephrine should be used with caution because it can lead to decreased stroke volumes despite improvement in mean arterial pressure. The Surviving Sepsis Campaign guidelines recommend it be used only as a salvage therapy or in cases where tachyarrhythmia prevents use of alternative vasopressor agents (see Table 50).

KEY POINTS

- Early and aggressive fluid resuscitation for patients with hypoperfusion resulting from sepsis begins with an initial bolus of 30 mL/kg body weight of crystalloid solution.
- Norepinephrine is recommended as the first vasopressor of choice for septic shock.

Antibiotic Therapy

Early antibiotic therapy is crucial in treating sepsis. Broad-spectrum antibiotics should be given within the first hour of suspected sepsis, and the regimen should be subsequently adjusted on the basis of culture results. Delay in the first dose of antibiotic therapy or use of inappropriate antibiotic therapy increases sepsis mortality. Although antibiotic stewardship is of paramount importance, the Surviving Sepsis Campaign guidelines recommend choosing up-front empiric therapy that is broad enough to cover the most likely pathogens causing sepsis. The most common pathogens include gram-negative, gram-positive, and "mixed" bacterial pathogens. However, treatment consideration should not be limited to bacterial coverage if empiric viral or fungal coverage are warranted. Consideration of the potential source of sepsis, local antibiotic resistance patterns, and a patient's clinical history (including the presence of an indwelling catheter, neutropenia, or another immunocompromised state) are important when choosing initial therapy. In addition, recent treatment with antibiotic therapy or a recent stay in a health care facility is associated with increased bacterial resistance and may necessitate broader empiric coverage compared with patients who do not have these risk factors. Guidelines do not provide specific recommendations about drug therapy, but the Surviving Sepsis Campaign guidelines do suggest that a carbapenem or extended-range penicillin or β-lactamase inhibitor may be a safe starting point in most septic patients. In cases of septic shock (but not sepsis without shock), combination therapy with at least two antibiotics from different classes should be employed against the most likely bacterial pathogen. In addition, when specific risks for multidrug resistance are present, empiric combination therapy against resistant gram-negative bacteria or targeted coverage of methicillin-resistant staph aureus is indicated. When available, the use of antibiograms specific to a community or healthcare facility is recommended to guide treatment.

Once a specific pathogen is identified, antibiotics should be tailored appropriately to the narrowest effective regimen. In many cases, culture data are either not obtained or remain negative. In these cases, deescalation of antibiotics is generally recommended within the first few days if a patient is improving clinically. Antibiotic therapy should usually be continued for 7 to 10 days, depending on the clinical situation. Antibiotics should also continually be reassessed for efficacy and opportunities for early deescalation or discontinuation sought. In patients with neutropenia, guidelines recommend that antibiotics be continued until either the full planned course of therapy concludes or the neutropenic state resolves (neutrophils higher than 500/μL [0.5×10^9/L]), whichever is later.

Prompt identification and control of potential sources of infection is essential in the management of sepsis. Examples include drainage of abscesses and removal of intravenous catheters suspected of being infected. One exception is necrotizing pancreatitis, for which definitive resection or drainage should be delayed until the extent of necrosis is clear.

The 2016 Surviving Sepsis Campaign guidelines suggest that procalcitonin, a serum marker for bacterial infection, may be used to support shortening the duration of antibiotic therapy in patients with sepsis or as a marker to support discontinuing therapy in patients who initially were thought to have sepsis but do not. Several recent meta-analyses support these guidelines, as they have demonstrated that algorithms that use procalcitonin as a decision support tool lead to decreased overall use of antibiotics. However, there remains conflicting evidence surrounding key outcome measures, including mortality benefit, associated with procalcitonin testing. This has led to wide heterogeneity among clinicians regarding whether procalcitonin is used in clinical practice.

KEY POINTS

- Prompt identification and control of any potential source of infection is essential in the management of sepsis.
- Broad-spectrum antibiotics should be given within the first hour of suspected sepsis, and the regimen subsequently adjusted based on culture results.
- In cases of septic shock, combination therapy with at least two antibiotics from different classes should be employed against the most likely bacterial pathogen.

Adjunctive Therapies

If possible, all patients receiving vasopressor therapy should have an arterial catheter for continuous blood pressure monitoring. Several large trials and meta-analyses have demonstrated that there is no benefit to using a pulmonary artery catheter to manage patients with septic shock. In many studies of pulmonary artery catheter use, patients with sepsis and septic shock demonstrated higher levels of resource use, higher complication rates, and in some cases higher mortality compared with no pulmonary artery catheter.

The use of glucocorticoids in the setting of sepsis has been suggested to achieve hemodynamic stability when it is not achieved using intravenous fluids and vasopressor therapies. Although there is not a clear mortality benefit, recent trials have showed that glucocorticoids are associated with a faster time to shock recovery and fewer days with organ failure or requirement for mechanical ventilation. Glucocorticoids have no role in sepsis without shock. The Society of Critical Care Medicine and the European Society of Intensive Care Medicine in 2017 recommended a maximum dose of 400 mg hydrocortisone daily, whereas the 2016 Surviving Sepsis Campaign guidelines recommend hydrocortisone to 200 mg daily for refractory shock. An adrenocorticotropic hormone stimulation test is not recommended.

Patients with sepsis or septic shock should receive early oral feeding when possible and should be considered at risk for malnutrition when in the ICU for more than 48 hours. If oral nutrition is not feasible, early enteral nutrition is indicated to minimize infectious complications associated with delayed enteral nutrition. In cases where both oral and enteral nutrition is not feasible, the optimal time and method to initiate parenteral therapy is not clear. New guidelines suggest, based largely on expert opinion, that caloric and protein needs should be gradually increased to their goal over the course of 3 to 7 days to avoid risks associated with early refeeding syndrome or overfeeding.

Glucose control is also important in patients with sepsis and septic shock. However, the optimal target is not entirely clear. In critically ill patients in a medical ICU, tight glucose control (for example, glucose 80-110 mg/dL) is associated with higher rates of severe hypoglycemia (glucose less than 40 mg/dL) and sometimes death compared with rates for similar patients managed with more liberal glucose targets (either 140-180 mg/dL or 180-200 mg/dL). The Surviving Sepsis Campaign Guidelines recommend targeting an upper glucose limit lower than 180 mg/dL in patients with sepsis and septic shock.

KEY POINTS

- Early enteral nutrition is recommended in septic patients, if possible.
- **HVC** The use of glucocorticoids in the setting of sepsis is suggested if adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability; there is no role for glucocorticoids in sepsis without shock.

Specific Critical Care Topics

Anaphylaxis

Anaphylaxis is a severe reaction caused by acute mediator release into the circulation, usually triggered by IgE-linked immunological responses to specific foods, medications, insect venom, latex, or other antigens but sometimes occurring without an allergic trigger. The mediator release results in various clinical manifestations such as pruritus, hypotension, and tissue swelling (known as angioedema) caused by capillary leak from widespread inflammatory mediator release (**Table 62**). Onset of symptoms may be immediate after antigen exposure or delayed, sometimes for hours or even days, although more rapid onset usually signals a more severe reaction. This capillary leak can result in distributive shock with many of the same features as septic shock. Angioedema can be life threatening when it compromises the airway.

Initial treatment is with epinephrine, which may be administered intramuscularly or intravenously. Adjunctive therapy with antihistamine medications may be used to relieve symptoms of pruritus and rash. Although they are commonly administered, evidence that glucocorticoids are useful in the treatment of anaphylaxis is sparse. Sometimes epinephrine must be given many times or continuously to achieve clinical stability. Patients should be given supplemental oxygen and watched closely for signs of airway compromise, which may require intubation to maintain airway patency. Patients often require fluid resuscitation, with or without vasopressor therapy. Removal of the precipitating antigen is also important if exposure is ongoing. Fortunately, anaphylaxis is rarely fatal, but successful management requires early recognition and prompt attention to supportive and disease-reversing therapies, especially when shock or airway compromise is present. Factors that increase risk for biphasic anaphylaxis (anaphylaxis occurring 1-72 hours after resolution of the initial episode) include a severe initial episode and a need for more than one dose of epinephrine. When such risk exists or when there is risk for anaphylaxis fatality resulting from coexisting cardiovascular disease or lack of access to epinephrine or emergency services, extended observation of up to 6 hours or longer may be warranted.

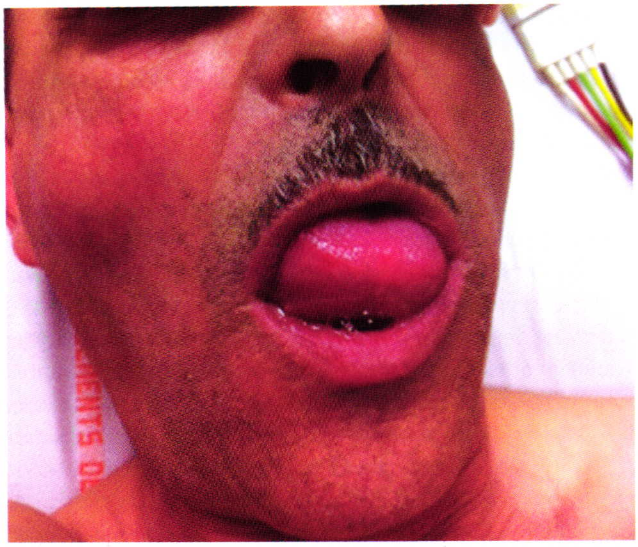


FIGURE 28. Angioedema of the tongue, bottom lip, and right side of the face with tongue protrusion on admission to the emergency department.

Reproduced with permission, from Arcani R, Martinez S, Gayet S. Sitagliptin and angioedema. Ann Intern Med. 2017;167:142-143. [PMID: 28554195] doi:10.7326/L16-0649. Copyright 2017, American College of Physicians.

Angioedema can occur without allergic stimulus (bradykinin-mediated), sometimes in response to medications (notably ACE inhibitors, even after long-term use) and sometimes for no identifiable reason. Nonallergic angioedema usually has slower onset and is not associated with urticaria, pruritus, or hypotension, but the tissue swelling can be clinically significant, especially in the airway (**Figure 28**), and may require intubation. Recurrent angioedema can be hereditary

TABLE 62. Organ System Involvement in Anaphylaxis

Organ System	Symptoms	Signs	Patients With Organ Involved
Skin and mucosa	Pruritus of skin, oropharynx, genitals, palms, soles	Flushing, urticaria, morbilliform rash, angioedema	85%
Respiratory	Dyspnea, chest and throat tightness, stridor, cough, hoarseness, sneezing, rhinorrhea	Wheeze, stridor, respiratory distress	70%
Cardiovascular	Lightheadedness, chest pain, palpitations	Hypotension, tachycardia > bradycardia	45%
Gastrointestinal	Pain, nausea, vomiting, diarrhea		45%
Neurologic	Anxiety, headache	Encephalopathy	15%

or acquired. Hereditary angioedema, which is distinct from the more typical mast cell–associated angioedema, is caused by activation of the complement cascade because of the lack or dysfunction of C1 esterase inhibitor. Hereditary angioedema may cause sporadic localized edema involving the head and neck and is differentiated from mast cell–associated angioedema by the lack of typical urticarial lesions. Diagnosis is by testing for quantitative and functional levels of C1 esterase inhibitor and C4 complement levels.

As in other forms of angioedema, treatment is supportive, sometimes with additional measures to control abnormal bradykinin, complement activation, or both.

KEY POINTS

- Initial treatment of anaphylaxis is with epinephrine, which may be administered intramuscularly or intravenously.
- Hereditary angioedema is caused by activation of the complement cascade because of the lack or dysfunction of C1 esterase inhibitor.

Hyperthermic Emergencies

Hyperthermic emergency is defined as the elevation of core body temperature, usually above 40 °C (104 °F), causing end-organ dysfunction or damage, which may include alteration in mental status, seizures, kidney injury, muscle rigidity, rhabdomyolysis, acute respiratory distress syndrome, and disseminated intravascular coagulation. Common causes of hyperthermia include heat stroke, malignant hyperthermia, and neuroleptic malignant syndrome, all of which can be fatal if not recognized and treated appropriately (**Table 63**).

Heat Stroke

Heat stroke occurs when the body's thermal regulatory system is overwhelmed by an environmental heat load. It is generally defined by a core body temperature above 40 °C (104 °F), along with encephalopathy. The elderly are particularly vulnerable, with added risk from comorbidities and medications. Exertional heat stroke can occur in young and otherwise healthy individuals, particularly when high ambient temperatures are combined with physical activity and high humidity. Extraneurologic complications can include kidney and liver injury, disseminated intravascular coagulation, and rhabdomyolysis.

If untreated, mortality in heat stroke can be up to 60%. Centrally acting antipyretics such as NSAIDs or acetaminophen are not effective. For patients with nonexertional heat stroke, evaporative cooling (water mist and fans) with or without ice packs can be used to lower the core temperature to a safe target level, usually 38.5 °C (101.0 °F). For exertional heat stroke, evaporative cooling may be effective, but patients who remain severely symptomatic despite evaporative cooling efforts sometimes require immersion in ice water to bring the core temperature down rapidly. Because immersion therapy may be complicated by hypothermia, it is not recommended as first-line treatment. In older patients with nonexertional hyperthermia, ice water immersion is associated with increased mortality and should not be used.

KEY POINT

- For patients with nonexertional heat stroke, evaporative cooling with or without ice packs can be used to lower the core temperature to a safe target level; for exertional heat stroke, immersion in ice water is sometimes required for severe cases.

Malignant Hyperthermia

Malignant hyperthermia occurs in people with a rare, autosomal dominant derangement in intracellular calcium metabolism that causes severe hyperthermia in response to inhaled

TABLE 63. Causes of Severe Hyperthermia

Diagnosis	Suggestive History	Key Examination Findings	Treatment	Notes
Heat stroke	Environmental exposure	Encephalopathy and fever	Evaporative cooling Ice water immersion	Avoid ice water immersion if nonexertional
Malignant hyperthermia	Exposure to volatile anesthetic or succinylcholine	Masseter muscle rigidity; ↑ arterial $P\text{CO}_2$	Stop inciting drug Dantrolene	Monitor and treat ↑ K^+ and ↑ arterial $P\text{CO}_2$
Neuroleptic malignant syndrome	Typical > atypical antipsychotic agent; onset over days to weeks	Altered mentation, severe rigidity, ↑ HR, ↑ BP, hyporeflexia, no clonus	Stop the inciting drug Dantrolene Bromocriptine	Resolves over days to weeks First symptom is usually change in mental status
Severe serotonin syndrome[a]	Onset within 24 hours of initiation or increasing SSRI dose, gastrointestinal prodrome	Agitation, myoclonus, ↑ reflexes, rigidity	Stop inciting drug Benzodiazepines Cyproheptadine	Resolves in 24 hours

BP = blood pressure; HR = heart rate; K^+ = potassium; SSRI = selective serotonin reuptake inhibitor.

[a] Not routinely considered a cause of severe hyperthermia but commonly confused with neuroleptic malignant syndrome.

anesthetic agents (such as halothane and isoflurane) or the depolarizing paralytic succinylcholine. Exposure to one of these agents may result in muscle rigidity, rhabdomyolysis, cardiac arrhythmias, and core body temperature elevation to 45 °C (113 °F) or greater. Mortality can reach 10%. Treatment consists of discontinuing the triggering agent, active cooling, and administration of the muscle relaxant dantrolene every 5 to 10 minutes until muscle rigidity and hyperthermia resolve.

Neuroleptic Malignant Syndrome and Serotonin Syndrome

Neuroleptic malignant syndrome is an idiosyncratic response classically associated with first-generation antipsychotic agents such as haloperidol, but it is also seen with newer-generation antipsychotics as well as antiemetics. It is more common at times of initiation or dose escalation but can occur after prolonged use. Highlighting a potential pathogenetic role for dopamine receptor blockade, it has also been described after rapid withdrawal of dopaminergic medications for Parkinson disease. The syndrome is characterized by the tetrad of fever, mental status changes, muscle rigidity, and dysautonomia. Mortality may exceed 10%. Treatment includes stopping the triggering agent (or reinstating the withdrawn dopaminergic agent), active cooling, and supportive care including IV fluid administration. Evidence for pharmacotherapy is anecdotal, but options include benzodiazepines, dantrolene, and bromocriptine. Neuroleptic medications can be reintroduced after a waiting period of at least 2 weeks, usually at lower dose, with care to avoid dehydration and concomitant administration with lithium.

Serotonin syndrome can present with mental status changes, dysautonomia, hyperthermia, hyperreflexia, and other muscle abnormalities. It is most commonly associated with selective serotonin reuptake inhibitors, but other drugs that affect serotonin signaling have been implicated. Management includes removing the offending agent and supportive care. Cyproheptadine is sometimes used off-label if benzodiazepines fail to control symptoms.

KEY POINT

- Treatment of neuroleptic malignant syndrome includes stopping the triggering agent, active cooling, and rehydration.

Accidental Hypothermia

Accidental hypothermia, defined by a core temperature below 35 °C (95 °F), is classically associated with winter in cold climates but can occur in more temperate weather if the exposure is sufficient (such as in wet conditions). In mild hypothermia, shivering is an effective compensatory mechanism, but in more severe cases (core temperature lower than 32 °C [89.6 °F]), it eventually ceases. Early signs of hypothermia include tachycardia, hyperventilation, poor judgment, and diuresis. Later findings include hypotension, bradycardia and other cardiac arrhythmias, and further depression of mental status with eventual coma (**Table 64**). In moderate to severe hypothermia, Osborne waves may be present on electrocardiogram tracings (**Figure 29**).

TABLE 64. Symptoms and Signs of Hypothermia

Severity	Core Temperature	Findings
Mild	32.0-35.0 °C (89.6-95.0 °F)	↑ HR, ↑ BP, ↑ RR, shivering, alert, poor judgment
Moderate	28.0-32.0 °C (82.4-89.6 °F)	↓ HR, ↓ BP, ↓ RR, ↓ CO, ↓O_2 consumption, ↓ kidney function, somnolence, no shivering, supraventricular arrhythmia
Severe	<28.0 °C (<82.4 °F)	Coma, absent reflexes, ventricular arrhythmia, asystole, apnea

BP = blood pressure; CO = cardiac output; HR = heart rate; RR = respiration rate.

If a severely hypothermic patient becomes pulseless and requires resuscitation, it is reasonable to continue cardiopulmonary resuscitation for a prolonged period until the patient can be rewarmed. There are reports of cardiopulmonary resuscitation lasting hours and resulting in full recovery when a severely hypothermic patient has a cardiac arrest.

Hypothermic patients who are shivering will passively rewarm themselves if they are removed from the cold environment and given adequate insulation to prevent heat loss. As core temperature drops below 32 °C (89.6 °F) and shivering stops, active rewarming should be implemented to prevent complications. Such techniques include surface methods, such as heating pads and forced-air warming systems, as well as invasive methods such as rewarming by peritoneal or pleural space irrigation using peritoneal catheters or thoracostomy tubes. Extracorporeal support, including cardiopulmonary bypass, is recommended for patients in cardiac arrest because it maximizes the rewarming rate and can provide hemodynamic support. During active rewarming, core temperature should be monitored with an esophageal temperature probe, as rectal and bladder temperatures will lag behind the rising core temperature during the rewarming process.

Toxicology

Alcohol Poisoning

Ethanol and other ingested alcohols activate the γ-aminobutyric acid receptor, which is the primary central nervous system

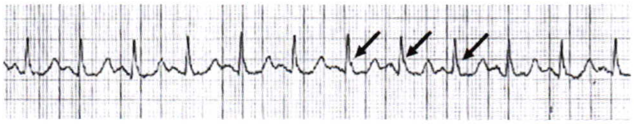


FIGURE 29. Electrocardiogram showing Osborne waves associated with hypothermia. They are best seen in the inferior and lateral chest leads. Osborne waves are defined by the shoulder or "hump" between QRS and ST segments.

TABLE 65. Presentation and Treatment of Alcohol Poisoning

Alcohol	Common Sources	Major Findings	Anion Gap	Osmolar Gap	Antidote
Ethanol	Alcoholic beverages	CNS depression Nausea, emesis	Possible	Yes	Supportive care
Isopropyl alcohol	Rubbing alcohol Disinfectants Antifreeze	CNS depression Ketone elevation	No	Yes	Supportive care
Methanol	Windshield wiper fluid De-icing solutions Solvents "Moonshine"	CNS depression Vision loss Hypotension	Yes	Yes	Fomepizole Ethanol (only if fomepizole is not available) HD for severe acidemia, very large ingestions, severe CNS depression, and any visual impairment
Ethylene glycol	Antifreeze De-icing solutions Solvents	CNS depression AKI Hypocalcemia Hypotension	Yes	Yes	Fomepizole Ethanol (only if fomepizole is not available) HD for severe acidemia, very large ingestions, severe CNS depression, AKI, and systemic collapse

AKI = acute kidney injury; CNS = central nervous system; HD = hemodialysis.

(CNS) inhibitor, thus leading to CNS depression, including loss of consciousness and suppression of respiratory drive at high doses, which can lead to respiratory failure or aspiration events.

Ethanol is the most commonly ingested alcohol and the most often encountered toxicity (**Table 65**). Other alcohols ingested include ethylene glycol (antifreeze), methanol (wood alcohol), and isopropyl alcohol (rubbing alcohol). These all have CNS depressant effects similar to those of ethanol. However, after ingestion, ethylene glycol is metabolized by alcohol dehydrogenase to oxalic acid, which crystallizes in the renal tubules and can lead to permanent kidney damage. Methanol is metabolized to formic acid, which is toxic to the retina and leads to blindness. When either of these alcohols has been ingested, there is an increased anion gap metabolic acidosis, as well as an increased osmolal gap (see MKSAP 19 Nephrology: Increased Anion Gap Metabolic Acidosis). Management includes competitive inhibition of alcohol dehydrogenase with intravenous fomepizole. If fomepizole is not available, intravenous ethanol also competes with other alcohols to reduce toxic metabolite formation. Hemodialysis rapidly and effectively removes alcohols and should be performed as soon as possible in confirmed ethylene glycol or methanol poisoning or in suspected cases associated with high anion gap metabolic acidosis or symptoms of end organ damage (visual impairment or kidney injury).

Isopropyl alcohol has no toxic metabolites and does not elevate the anion gap, although it does increase the osmolal gap. Treatment for ethanol and isopropyl toxicity is supportive.

KEY POINTS

- Ethylene glycol and methanol ingestion are associated with an increased anion gap metabolic acidosis as well as an increased osmolal gap.
- Management of ethylene glycol and methanol ingestion includes competitive inhibition of alcohol dehydrogenase with intravenous fomepizole.
- Hemodialysis rapidly and effectively removes alcohols and should be performed as soon as possible in confirmed ethylene glycol or methanol poisoning or in suspected cases associated with high anion gap metabolic acidosis or symptoms of end organ damage.

Carbon Monoxide Poisoning

Carbon monoxide (CO) is a colorless, odorless product of hydrocarbon combustion that is readily absorbed into the circulation when inhaled and binds avidly to hemoglobin to form carboxyhemoglobin, displacing oxygen and causing tissue hypoxia and ischemia. CO toxicity occurs almost exclusively in enclosed areas where combustion is occurring and is often accidental, but it may be intentional in suicide attempts. Exposed patients present with headache, nausea, malaise, confusion, syncope, seizures, or coma. Patients with coronary artery disease may develop signs and symptoms of cardiac ischemia.

Pulse oximetry is not helpful, as current transcutaneous oximetry technology does not differentiate between oxyhemoglobin and carboxyhemoglobin. Blood gas analysis, including CO oximetry, will provide the carboxyhemoglobin level, which is less than 3% in normal individuals. Smokers may have up to 10% to 15% carboxyhemoglobin; anything higher is consistent with CO poisoning.

Because oxygen and CO competitively bind to hemoglobin, the primary treatment is supplemental oxygen. Once the CO exposure has been stopped, the half-life of carboxyhemoglobin is 300 minutes if patients are breathing ambient air, 90 minutes if breathing 100% oxygen, and 30 minutes if given hyperbaric oxygen in a chamber where the pressure is gradually increased to 2 to 3 times the normal atmospheric pressure. Patients with high levels of carboxyhemoglobin (25% and greater) and evidence of organ ischemia should be treated with hyperbaric oxygen if possible.

In addition to the immediate complications resulting from tissue hypoxia in the setting of CO toxicity, there are also delayed neurologic sequelae in approximately 40% of severe cases of CO poisoning. The mechanism is poorly understood, but probably relates to ischemic damage sustained in specific, oxygen-sensitive areas of the brain. These delayed neurocognitive and personality defects usually appear within 20 days of the exposure, but they can appear later and may last for a year or longer. There is weak evidence that hyperbaric oxygen therapy reduces the risk and severity of these delayed neurologic sequelae.

KEY POINTS

HVC
- Pulse oximetry is not helpful in diagnosing carbon monoxide poisoning, as it does not differentiate between oxyhemoglobin and carboxyhemoglobin.
- Patients with high levels of carboxyhemoglobin (25% or higher) and evidence of organ dysfunction should be treated with hyperbaric oxygen if possible.

Cyanide Poisoning

Cyanide is one of the most lethal poisons known. It inhibits cellular respiration by binding to cytochrome oxidase a_3 in the mitochondria, blocking the cells' ability to use oxygen for aerobic metabolism. This results in clinical signs of hypoxia, despite normal oxyhemoglobin saturation. Symptoms often include headache, anxiety, nausea, and either a metallic or bitter almond odor and taste. More severe or prolonged exposure can lead to coma, seizures, liver or kidney injury, vomiting, ischemic pain, rhabdomyolysis, and death. Serum lactate elevation is a sensitive but nonspecific marker for cyanide toxicity. A normal lactate concentration effectively rules out significant cyanide exposure.

Cyanide can be ingested or inhaled and is absorbed readily and acts quickly to inhibit cellular metabolism. Inhalation exposure is common in house fires, where cyanide is produced and aerosolized when vinyl burns. Cyanide is a common coexposure with CO. Prolonged nitroprusside infusion may also result in cyanide toxicity.

Successful treatment depends on early recognition of cyanide toxicity, elimination of ongoing exposure (e.g., removal of contaminated clothing), and either neutralization or competitive binding of the cyanide to remove it from the mitochondrial respiration system. Hydroxocobalamin avidly binds to cyanide to produce cyanocobalamin, which is soluble, nontoxic, and readily excreted. The usual dose is 5 g for an adult. Other antidotes include nitrites (amyl nitrite and sodium nitrite) to induce methemoglobin, which in turn binds cyanide, as well as sodium thiosulfate, which donates sulfur to combine with cyanide, producing harmless thiocyanate. Inducing methemoglobinemia in inhalation injury victims who may also have high levels of carboxyhemoglobin is not safe, so nitrite therapy should be avoided. Of these potential treatment strategies, hydroxocobalamin is the most commonly recommended because of the ease and safety of administration.

TABLE 66. Toxic Syndromes and Their Manifestations

Syndrome	Manifestations	Representative Drugs
Sympathomimetic	Tachycardia Hypertension Diaphoresis Agitation Seizures Mydriasis	Cocaine Amphetamines Ephedrine Caffeine
Cholinergic	"SLUDGE" (salivation, lacrimation, increased urination and defecation, gastrointestinal upset, and emesis) Confusion Bronchorrhea Bradycardia Miosis	Organophosphates (insecticides, sarin) Carbamates Physostigmine Edrophonium Nicotine
Anticholinergic	Hyperthermia Dry skin and mucous membranes Agitation, delirium Tachycardia, tachypnea Hypertension Mydriasis	Antihistamines Tricyclic antidepressants Anti-Parkinson agents Atropine Scopolamine
Opioids	Miosis Respiratory depression Lethargy, confusion Hypothermia Bradycardia Hypotension	Morphine, fentanyl, oxycodone and related drugs Heroin

KEY POINT

- Successful treatment of cyanide poisoning depends on early recognition of cyanide toxicity, elimination of ongoing exposure, and administration of hydroxocobalamin to remove the cyanide from the mitochondrial respiration system.

Toxicity of Drugs of Abuse

Drugs of abuse may be taken singly or in combination, and an accurate history may be impossible to obtain as a result of alteration of mental status, reluctance on the part of the patient to disclose drug use, and insufficient or incorrect knowledge about the composition of such drugs. Clinical toxic syndromes, or constellations of symptoms and signs indicative of certain classes of drugs, can be recognized and provide clues as to what should be done for effective medical management of overdose (**Table 66** and **Table 67**).

In addition to seeking to identify the specific agents or classes of drugs taken, care of overdose patients is primarily supportive; maintenance of airway patency and ventilation is critically important in patients with decreased mental status. Patients may need intubation to protect the airway from aspiration or in cases of respiratory failure where respiratory drive is impaired by drugs.

An early empiric trial of the opioid antagonist naloxone is warranted when opioid overdose is suspected to reverse respiratory depression and depressed mental status. When used, it should be titrated to adequate respiratory rate and not to mental status. It is important to remember that naloxone has a very short half-life, and its antidote effects will usually wear off before the opioid effects are gone. Patients should be observed for signs of opioid withdrawal (which is not fatal and requires only supportive care) and for continued or recurrent signs of respiratory distress, which may require repeated dosing of naloxone.

Administration of flumazenil for suspected benzodiazepine overdose is more problematic, as reversing the effect of benzodiazepines can lead to life-threatening CNS activation, including seizures, which are most likely in patients receiving benzodiazepines chronically. It is usually best to manage patients with ventilator support and allow elimination of the agent over time.

In patients who have received sympathomimetic agents, such as cocaine or amphetamines, benzodiazepines are the cornerstone of therapy for agitation. β-Blocker medications should be avoided, as they will block the beta-adrenergic receptors and, at least theoretically, leave the activated alpha receptors unopposed, thus leading to severe hypertension.

TABLE 67. Presentation and Management of Some Drugs of Abuse

Drug Class	Examples	Examination Findings	Antidote
Opioids	Heroin, oxycodone, fentanyl analogs	↓ HR, ↓ temp, ↓ BP, ↓ RR, miosis	Naloxone
Benzodiazepines	Lorazepam	CNS depression, usually normal vital signs and eye examination	Flumazenil (not generally recommended; may be complicated by seizure)
Sympathomimetics	All	↑ HR, ↑ BP, ↑ temp, diaphoresis, mydriasis, agitation, seizure, ↑ CK, ↑ liver chemistry studies, ↑ Cr	Benzodiazepines are first-line for agitation; avoid β-blockers for hypertension; haloperidol may worsen hyperthermia
	Specific drugs:		
	Cocaine	Myocardial infarction prominent; 30-minute duration	
	Methamphetamine	Violent agitation prominent; ↓ Na; 20-hour duration	
	MDMA ("ecstasy")	↓ Na, serotonin syndrome	
	Bath salts ("plant food")	Hallucinations, violent agitation common; duration up to 48 hours; negative urine drug screen	
Hallucinogens	Dextromethorphan	↑ HR, ↑ BP, agitation, coma	
	Lysergic acid diethylamide (LSD)	Mild ↑ HR; ↑ BP; rare ↑ temp and hemodynamic instability	Benzodiazepines are first-line for agitation
			Haloperidol is second-line
	Phencyclidine (PCP)	Variable mental status: ↑ agitation, CNS depression, nystagmus	
	Synthetic cannabinoids ("Spice," "K-2")	↑ HR; greater agitation than with marijuana; ↑ Cr; negative urine drug screen	

BP = blood pressure; CK = creatine kinase; CNS = central nervous system; Cr = creatinine; HR = heart rate; MDMA = 3-4 methylenedioxymethamphetamine; Na = sodium; RR = respiration rate; temp = temperature.

Hallucinogenic agents have no antidote, so care is supportive, including maintaining the airway, ventilation, and hemodynamic support. These patients may be extremely agitated and combative, requiring physical restraints or sedation to prevent them from harming themselves and others.

Overdose of Therapeutic Drugs

Patients may overdose on prescribed medications either inadvertently or intentionally, and often many medications are taken together, sometimes with alcohol. Information about suicidal ideation or intent, what medications a patient and family members have been prescribed, what prescriptions were filled, events reported by the patient or bystanders, and clinical signs and symptoms are all important in determining the nature of an overdose (**Table 68**). If patients are alert and cooperative enough to protect their airway, administration of activated charcoal may be beneficial if it can be given within 1 to 2 hours of ingestion. Acetaminophen overdose is discussed in MKSAP 19 Gastroenterology and Hepatology, and salicylate overdose in MKSAP 19 Nephrology.

Acute Abdominal Surgical Emergencies

A large number of conditions can cause abdominal pain, distention, and rigidity. Although many of them can and should be managed medically, some require surgery, and timely diagnosis followed by surgical intervention is needed to improve survival. Imaging decisions should be based on history and examination findings, and they should not delay intervention (**Table 69**). For further discussion of abdominal compartment syndrome see MKSAP 19 Nephrology.

TABLE 68. Presentation and Treatment of Therapeutic Drug Toxicities

Medication	Key Clinical Findings	Treatment	Notes
Nonopioid analgesics			
Acetaminophen	↑ liver chemistry studies, ↑ Cr, ↑ INR, encephalopathy, cerebral edema, vomiting	*N*-acetylcysteine	Transfer to liver transplant center if severe
Salicylates	Mixed respiratory alkalosis/anion gap metabolic acidosis, tinnitus, agitation, confusion, hyperthermia	Forced diuresis, bicarbonate infusion, glucose	Target urine pH 7.5-8.0; hemodialysis if acute kidney injury or severe toxicity
Cardiovascular			
β-Blocker, calcium channel blocker	↓ HR, ↓ BP, heart block; altered mental status if β-blocker	Atropine 1 mg IV up to 3 doses, glucagon, calcium chloride, vasopressors, cardiac pacemaker (if indicated), high-dose insulin and glucose, IV lipid emulsion	Treatments may be added sequentially or initiated simultaneously depending on severity of case and response to treatment
Digoxin	↓ HR, arrhythmia, nausea, emesis, abdominal pain, confusion, weakness	Digoxin-specific antibody	Use of antibody lowers K^+; hemodialysis not effective
Anticholinergics			
Tricyclic antidepressants	↓ BP, sedation, seizure, anticholinergic signs, prolonged QRS, arrhythmia	Bicarbonate infusion titrated to QRS duration; benzodiazepines for seizure	Physostigmine contraindicated
Antihistamines	Anticholinergic signs, including agitation and seizures	Benzodiazepines; physostigmine if isolated anticholinergic overdose	Physostigmine use requires continuous cardiac monitor and bedside atropine
Hypoglycemic			
Sulfonylurea	↓ glucose, confusion, seizure, anxiety, diaphoresis, tremor	IV glucose + octreotide, glucagon IM = temporizing	Monitor for ↓ glucose for 48 hours if large ingestion
Metformin	↑ lactate, abdominal pain	Hemodialysis for severe ↓ pH or acute kidney injury	Glucose usually normal if isolated metformin ingestion
Others			
Lithium	GI distress, confusion, ataxia, tremor, myoclonic jerks, diabetes insipidus	Hemodialysis if lithium level >4 mEq/L (4 mmol/L) or severe symptoms	Serum level can guide need for hemodialysis, confirm diagnosis
SSRI/SNRI	Agitation, myoclonus, ↑ reflexes, rigidity, fever, ↑ HR	Benzodiazepines, cyproheptadine if severe	Venlafaxine has ↑ cardiac toxicity

BP = blood pressure; Cr = creatinine; GI = gastrointestinal; HR = heart rate; IM = intramuscular; IV = intravenous; K^+ = potassium; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

TABLE 69. Acute Abdominal Emergencies

Diagnosis	Presentation	Diagnostic Imaging	Notes
Acute cholecystitis and cholangitis	Persistent peritoneal RUQ or epigastric pain, fever, emesis, positive Murphy sign	Ultrasonography EUS and ERCP for diagnosis and treatment of cholangitis	↑ alkaline phosphatase, ↑ bilirubin suggests cholangitis but typically not cholecystitis
Bowel obstruction	Cramping pain, emesis, distention, obstipation, dehydration	Radiography: dilated loops of bowel with air-fluid levels CT: identifies cause, complications	Top causes: incarcerated hernia, adhesions, volvulus, intussusception
Acute appendicitis	Classic: periumbilical then RLQ pain, emesis, ↑ leukocyte count	Often unnecessary CT or ultrasonography if unclear	Pain quality and location vary with appendix location
Peptic ulcer perforation	Abrupt peritoneal pain, later distention and hypovolemia	Radiography: free air CT if unclear	Surgery necessary in majority of cases
Acute mesenteric ischemia	Pain out of proportion to examination findings, vomiting, hypotension, risk factors for thrombosis, embolism	CT angiography or conventional arteriography	↑ amylase, ↑ phosphate common Regular CT and lactate can be normal early in course
Toxic megacolon	Pain, diarrhea, fever, ↑ HR, ↓ BP, confusion	Radiography: dilated colon, air-fluid levels in colon CT if unclear	Causes: inflammatory bowel disease, *Clostridioides difficile* infection
Ruptured abdominal aortic aneurysm	↓ BP, abdominal and/or flank pain, pulsatile mass	Unnecessary if high suspicion and unstable CT or ultrasonography if unclear	Risk factors: older age, male, smoking, hypertension, family history of aneurysm
Ectopic pregnancy with tubal rupture	↓ BP, ↓ Hb, ↑ hCG, abdominal pain, vaginal bleeding	Transvaginal ultrasonography	High mortality without early surgery

BP = blood pressure; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasonography; Hb = hemoglobin; hCG = human chorionic gonadotropin; HR = heart rate; RLQ = right lower quadrant; RUQ = right upper quadrant; temp = temperature.

Fat Embolism

Fat embolism is the entrance of fat globules in the systemic circulation. It is a relatively common occurrence after trauma involving long bone fractures. Fat embolism syndrome, however, is a rare but potentially lethal complication resulting from systemic manifestations of fat emboli when they lodge in capillaries and arterioles. It is a clinical diagnosis centered on the presence of a triad of respiratory insufficiency, neurologic dysfunction, and petechial rash in the appropriate clinical setting. High-resolution CT findings are nonspecific, and imaging may be normal. There is no definitive therapy for established fat embolism syndrome. Treatment is supportive, and most patients recover spontaneously and completely, although mortality can be as high as 5% to 20%.

Approach to the Critically Ill Patient Who Is Pregnant

The physiologic changes in pregnancy present a unique challenge to the management of these patients in the critical care setting. Optimization of maternal physiology without compromising the well-being of the fetus requires a multidisciplinary approach involving an intensivist, an obstetrician-gynecologist, and a neonatologist. Particular attention must be given to the pharmacology of medications, including the potential for fetal exposure from transfer across the placenta.

The most frequent critical care emergencies in pregnancy are summarized in **Table 70**.

Encephalopathy

Alterations in mental status are common in the ICU because of both critical illness and the ICU environment, which is disruptive to sleep and inhibits contextual clues for orientation to time, place, and events. Many conditions involve mental status change, but three are most important in the context of critical care medicine: delirium (addressed in Principles of Critical Care), coma, and anoxic brain injury.

Coma

Coma describes a condition of absent cortical function of the CNS with intact brainstem function, whether a result of illness, trauma, or medication. Patients in a coma do not respond to external stimuli. The Glasgow Coma Scale is an instrument for assessing the severity of deficit based on three categories of stimulus response: eye response, verbal response, and motor response (**Table 71**). A Glasgow Coma Scale score of 15 means a normal, alert (or fully arousable) patient, and a score of 3 means no response at all. Physical examination findings of brainstem (pupil or eye movement) or motor (posturing) abnormalities might help localize disease in the CNS. In addition to a clinical examination,

TABLE 70. Obstetric Critical Care Emergencies

Presentation	Causes	Diagnosis	Key Treatment Principles
Dyspnea	Status asthmaticus	Diagnosis based on clinical presentation	Inhaled glucocorticoids (preferentially budesonide or fluticasone); short-acting β_2 agonists and short courses of systemic glucocorticoids can be used. Intubation and mechanical ventilation if needed
	Venous thromboembolism	Ultrasonography if DVT suspected, ventilation/perfusion scan, CT pulmonary angiography	Low-molecular-weight-heparin therapy recommended
	Pneumonia	Chest radiography	Avoid fluoroquinolones and tetracyclines Treat exposure to influenza with oseltamivir
	Pulmonary edema; specific obstetric etiologies: preeclampsia, tocolytic therapy, peripartum cardiomyopathy	Chest radiography, echocardiogram, invasive hemodynamic monitoring if needed	Furosemide Nitroglycerine, hydralazine or calcium channel blockers for preload/afterload reduction
	ARDS; specific obstetric etiologies to consider: amniotic fluid embolism, acute fatty liver of pregnancy, intrauterine infections		Intubation and mechanical ventilation if needed Evaluation for delivery No controlled data on safety of permissive hypercapnia, fluid-restrictive strategy, or prone positioning in pregnancy
Hemorrhage	Antepartum etiologies: abruptio placentae, placenta previa, uterine rupture Postpartum hemorrhage: uterine atony, retained placenta	Abruptio placentae: clinical diagnosis (abrupt vaginal bleeding, back pain, contractions) Placenta previa diagnosed with ultrasonography (transabdominal/transvaginal) Uterine rupture: clinical diagnosis (vaginal bleeding, abdominal pain, shock, fetal compromise typically during labor)	Resuscitation with fluids and blood products Correct coagulopathy Consideration to delivery Refractory bleeding: embolization/surgical exploration Hysterectomy
Hypertension	Preeclampsia (hypertension with proteinuria after 20 weeks' gestation)	Clinical diagnosis; severe cases with evidence of end-organ dysfunction	Consideration to delivery Magnesium sulfate (to prevent eclampsia) Antihypertensives (labetalol, hydralazine, nifedipine)
Seizure	Eclampsia	Clinical diagnosis: new-onset seizures in a patient with preeclampsia	Maternal hemodynamic and respiratory support Magnesium sulfate Antihypertensives (labetalol, hydralazine, nicardipine) Delivery

ARDS = acute respiratory distress syndrome; DVT = deep venous thrombosis.

lumbar puncture and CNS imaging with MRI or CT scan are useful in diagnosing the cause of coma. Treatment is supportive with efforts to reverse the specific cause of the coma if possible.

Anoxic Brain Injury

Anoxic brain injury refers to damage to the CNS caused by prolonged, profound tissue hypoxia. There are many possible causes of such hypoxia, including near drowning, seizures,

TABLE 71. Glasgow Coma Scale

Response	Score
Eyes	
Does not open eyes	1
Opens eyes in response to painful stimuli (when given pain)	2
Opens eyes in response to voice	3
Opens eyes spontaneously	4
Verbal	
Makes no sound	1
Incomprehensible sounds (mumbles)	2
Utters inappropriate words	3
Confused, disorientated	4
Oriented, chats normally	5
Motor (physical reflexes)	
Makes no movements	1
Extension (straightens limb when given painful stimulus)	2
Abnormal flexion (flexes limbs indiscriminately when given painful stimulus)	3
Flexion/withdrawal to painful stimuli (moves away when given painful stimulus)	4
Localizes painful stimuli (can pinpoint where pain is)	5
Obeys commands	6
Brain Injury Classification Based on Score	**Total Score (Eyes + Verbal + Motor)**
Coma	3-8
Moderate brain injury	9-12
Mild brain injury	13-15

obstructed airway, lung disease, cardiac arrest, asphyxiation, and other inhalational injury. Brain imaging shows edema and loss of grey-white matter demarcation. Electroencephalographic monitoring shows various patterns, from diffuse slowing (typical of many types of encephalopathy) to burst suppression or seizure activity (indicative of more severe injury) to absence of brain electrical activity (which can indicate brain death). Prognosis is often not immediately apparent, and patients with anoxic brain injury require supportive care for 3 to 5 days or longer before the extent of injury can be understood well enough to be declared irreversible.

KEY POINT

- Prognosis for patients with anoxic brain injury is often not immediately apparent, and patients require supportive care for 3 to 5 days or longer before the extent of injury can be understood well enough to be declared irreversible.

Bibliography

Pulmonary Diagnostic Tests

Counts SJ, Kim AW. Diagnostic imaging and newer modalities for thoracic diseases: PET/Computed tomographic imaging and endobronchial ultrasound for staging and its implication for lung cancer. Surg Clin North Am. 2017;97:733-750. [PMID: 28728712] doi:10.1016/j.suc.2017.03.012

Dempsey TM, Scanlon PD. Pulmonary function tests for the generalist: A brief review. Mayo Clin Proc. 2018;93:763-771. [PMID: 29866281] doi:10.1016/j.mayocp.2018.04.009

Little BP. Approach to chest computed tomography. Clin Chest Med. 2015;36:127-45, vii. [PMID: 26024596] doi:10.1016/j.ccm.2015.02.001

Rambhia SH, D'Agostino CA, Noor A, et al. Thoracic ultrasound: technique, applications, and interpretation. Curr Probl Diagn Radiol. 2017 Jul-Aug;46:305-316. [PMID: 28185691] doi:10.1067/j.cpradiol.2016.12.003

Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease [Editorial]. Eur Respir J. 2014;44:1447-78. [PMID: 25359356] doi:10.1183/09031936.00150414

Wang Z, Pianosi PT, Keogh KA, et al. The diagnostic accuracy of fractional exhaled nitric oxide testing in asthma: A systematic review and meta-analyses. Mayo Clin Proc. 2018;93:191-198. [PMID: 29275031] doi:10.1016/j.mayocp.2017.11.012

Airways Disease

Beasley R, Holliday M, Reddel HK, et al; Novel START Study Team. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med. 2019;380:2020-2030. [PMID: 31112386] doi:10.1056/NEJMoa1901963

Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA. 2020;324:2301-2317. [PMID: 33270095] doi:10.1001/jama.2020.21974

Global Initiative for Asthma. Global strategy for asthma management and prevention, 2021. Accessed May 5, 2021. https://ginasthma.org/gina-reports/

Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report. Accessed September 27, 2020. https://goldcopd.org/gold-reports/

Hill AT, Sullivan AL, Chalmers JD, et al. British Thoracic Society guideline for bronchiectasis in adults. BMJ Open Respir Res. 2018;5:e000348. [PMID: 30687502] doi:10.1136/bmjresp-2018-000348

Ramsahai JM, Hansbro PM, Wark PAB. Mechanisms and management of asthma exacerbations. Am J Respir Crit Care Med. 2019;199:423-432. [PMID: 30562041] doi:10.1164/rccm.201810-1931CI

Rusznak M1, Peebles RS. Aspirin-exacerbated respiratory disease. N Engl J Med. 2018 Dec 6;379(23):2280-2281.

Skloot GS, Busse PJ, Braman SS, et al; ATS ad hoc Committee on Asthma in the Elderly. An official american thoracic society workshop report: evaluation and management of asthma in the elderly. Ann Am Thorac Soc. 2016; 13:2064-2077. [PMID: 27831798]

Siu AL, Bibbins-Domingo K, Grossman DC, et al; US Preventive Services Task Force (USPSTF). Screening for chronic obstructive pulmonary disease: US preventive services task force recommendation statement. JAMA. 2016;315:1372-7. [PMID: 27046365] doi:10.1001/jama.2016.2638

Walshaw MJ. Cystic fibrosis: diagnosis and management-NICE guideline 78. Paediatr Respir Rev. 2019;31:12-14. [PMID: 30962150] doi:10.1016/j.prrv.2019.02.006

Diffuse Parenchymal Lung Disease

Belloli EA, Beckford R, Hadley R, et al. Idiopathic non-specific interstitial pneumonia. Respirology. 2016;21:259-68. [PMID: 26564810] doi:10.1111/resp.12674

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. an international working group report. Am J Respir Crit Care Med. 2016;194:265-75. [PMID: 27299520] doi:10.1164/rccm.201604-0801CI

Kumar A, Cherian SV, Vassallo R, et al. Current concepts in pathogenesis, diagnosis, and management of smoking-related interstitial lung diseases. Chest. 2018;154:394-408. [PMID: 29222007] doi:10.1016/j.chest.2017.11.023

Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378:1811-1823. [PMID: 29742380] doi:10.1056/NEJMra1705751

Mira-Avendano I, Abril A, Burger CD, et al. Interstitial lung disease and other pulmonary manifestations in connective tissue diseases. Mayo Clin Proc. 2019;94:309-325. [PMID: 30558827] doi:10.1016/j.mayocp.2018.09.002

Noe MH, Rosenbach M. Cutaneous sarcoidosis. Curr Opin Pulm Med. 2017; 23:482-486. [PMID: 28598873] doi:10.1097/MCP.0000000000000402

Raghu G, Remy-Jardin M, Myers JL, et al; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis. an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198:e44-e68. [PMID: 30168753] doi:10.1164/rccm.201807-1255ST

Raghu G, Rochwerg B, Zhang Y, et al; American Thoracic Society. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. an update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3-19. [PMID: 26177183] doi:10.1164/rccm.201506-1063ST

Tomassetti S, Ravaglia C, Poletti V. Diffuse parenchymal lung disease. Eur Respir Rev. 2017;26. [PMID: 28446601] doi:10.1183/16000617.0004-2017

Witt LJ, Curran JJ, Strek ME. The diagnosis and treatment of antisynthetase syndrome. Clin Pulm Med. 2016;23:218-226. [PMID: 27594777]

Yoon HY, Kim TH, Seo JB, et al. Effects of emphysema on physiological and prognostic characteristics of lung function in idiopathic pulmonary fibrosis. Respirology. 2019;24:55-62. [PMID: 30136753] doi:10.1111/resp.13387

Occupational Lung Disease

Bacchus L, Shah RD, Chung JH, et al; Expert Panel on Thoracic Imaging. ACR appropriateness criteria review ACR appropriateness criteria® occupational lung diseases. J Thorac Imaging. 2016;31:W1-3. [PMID: 26656194] doi:10.1097/RTI.0000000000000194

De Matteis S, Heederik D, Burdorf A, et al; European Respiratory Society Environment and Health Committee. Current and new challenges in occupational lung diseases. Eur Respir Rev. 2017;26. [PMID: 29141963] doi:10.1183/16000617.0080-2017

Perlman DM, Maier LA. Occupational lung disease. Med Clin North Am. 2019;103:535-548. [PMID: 30955520] doi:10.1016/j.mcna.2018.12.012

Seaman DM, Meyer CA, Kanne JP. Occupational and environmental lung disease. Clin Chest Med. 2015;36:249-68, viii-ix. [PMID: 26024603] doi:10.1016/j.ccm.2015.02.008

van der Molen HF, de Groene GJ, Hulshof CTJ, et al. Association between work and chronic obstructive pulmonary disease (COPD). J Clin Med. 2018;7. [PMID: 30304764] doi:10.3390/jcm7100335

Pleural Disease

Dugan KC, Laxmanan B, Murgu S, et al. Management of persistent air leaks. Chest. 2017;152:417-423. [PMID: 28267436] doi:10.1016/j.chest.2017.02.020

Feller-Kopman D, Light R. Pleural disease. N Engl J Med. 2018;378:740-751. [PMID: 29466146] doi:10.1056/NEJMra1403503

Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of malignant pleural effusions. an official ATS/STS/STR clinical practice guideline. Am J Respir Crit Care Med. 2018;198:839-849. [PMID: 30272503] doi:10.1164/rccm.201807-1415ST

Iyer NP, Reddy CB, Wahidi MM, et al. Indwelling pleural catheter versus pleurodesis for malignant pleural effusions. A systematic review and meta-analysis. Ann Am Thorac Soc. 2019;16:124-131. [PMID: 30272486] doi:10.1513/AnnalsATS.201807-495OC

Khemasuwan D, Sorensen J, Griffin DC. Predictive variables for failure in administration of intrapleural tissue plasminogen activator/deoxyribonuclease in patients with complicated parapneumonic effusions/empyema. Chest. 2018;154:550-556. [PMID: 29425674] doi:10.1016/j.chest.2018.01.037

Nayak R, Brogly SB, Lajkosz K, et al. Outcomes of operative and nonoperative treatment of thoracic empyema: A population-based study. Ann Thorac Surg. 2019;108:1456-1463. [PMID: 31356799] doi:10.1016/j.athoracsur.2019.05.090

Patil M, Dhillon SS, Attwood K, et al. Management of benign pleural effusions using indwelling pleural catheters: A systematic review and meta-analysis. Chest. 2017;151:626-635. [PMID: 27845052] doi:10.1016/j.chest.2016.10.052

Semenkovich TR, Olsen MA, Puri V, et al. Current state of empyema management. Ann Thorac Surg. 2018;105:1589-1596. [PMID: 29550205] doi:10.1016/j.athoracsur.2018.02.027

Tschopp JM, Bintcliffe O, Astoul P, et al. ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. Eur Respir J. 2015; 46:321-35. [PMID: 26113675] doi:10.1183/09031936.00219214

Wilcox ME, Chong CA, Stanbrook MB, et al. Does this patient have an exudative pleural effusion? The Rational Clinical Examination systematic review. JAMA. 2014;311:2422-31. [PMID: 24938565] doi:10.1001/jama.2014.5552

Pulmonary Vascular Disease

Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J. 2019;53:1801904. doi:10.1183/13993003.01904-2018

Galiè N, Humbert M, Vachiery JL, et al; ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37:67-119. [PMID: 26320113] doi:10.1093/eurheartj/ehv317

Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53. [PMID: 30545969] doi:10.1183/13993003.01915-2018

Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report. Chest. 2019;155:565-586. [PMID: 30660783] doi:10.1016/j.chest.2018.11.030

Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53. [PMID: 30545968] doi:10.1183/13993003.01913-2018

Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913. doi:10.1183/13993003.01913-2018

Lung Tumors

Carter BW, Marom EM, Detterbeck FC. Approaching the patient with an anterior mediastinal mass: a guide for clinicians. J Thorac Oncol. 2014;9:S102-9. [PMID: 25396306] doi:10.1097/JTO.0000000000000294

Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e93S-e120S. [PMID: 23649456] doi:10.1378/chest.12-2351

Kindler HL, Ismaila N, Armato SG 3rd, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36:1343-1373. [PMID: 29346042] doi:10.1200/JCO.2017.76.6394

MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

Sholl LM. Biomarkers in lung adenocarcinoma: a decade of progress. Arch Pathol Lab Med. 2015;139:469-80. [PMID: 25255293] doi:10.5858/arpa.2014-0128-RA

Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e211S-e250S. [PMID: 23649440] doi:10.1378/chest.12-2355

Sleep Medicine

Caples SM, Rowley JA, Prinsell JR, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. Sleep. 2010;33:1396-407. [PMID: 21061863]

Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373:1095-105. [PMID: 26323938] doi:10.1056/NEJMoa1506459

Hudgel DW, Patel SR, Ahasic AM, et al; American Thoracic Society Assembly on Sleep and Respiratory Neurobiology. The role of weight management in the treatment of adult obstructive sleep apnea. an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2018;198:e70-e87. [PMID: 30215551] doi:10.1164/rccm.201807-1326ST

Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13:479-504. [PMID: 28162150] doi:10.5664/jcsm.6506

Mokhlesi B, Masa JF, Brozek JL, et al. Evaluation and management of obesity hypoventilation syndrome. an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2019;200:e6-e24. [PMID: 31368798] doi:10.1164/rccm.201905-1071ST

Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2019;15:301-334. [PMID: 30736888] doi:10.5664/jcsm.7638

Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med. 2015;11:773-827. [PMID: 26094920] doi:10.5664/jcsm.4858

High-Altitude–Related Illnesses

Ahmedzai S, Balfour-Lynn IM, Bewick T, et al; British Thoracic Society Standards of Care Committee. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. Thorax. 2011;66 Suppl 1:i1-30. [PMID: 21856702] doi:10.1136/thoraxjnl-2011-200295

Bärtsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. N Engl J Med. 2013;368:2294-302. [PMID: 23758234] doi:10.1056/NEJMcp1214870

Ergan B, Akgun M, Pacilli AMG, et al. Should I stay or should I go? COPD and air travel. Eur Respir Rev. 2018;27. [PMID: 29898904] doi:10.1183/16000617.0030-2018

Hu X, Cowl CT, Baqir M, et al. Air travel and pneumothorax. Chest. 2014;145:688-694. [PMID: 24687705] doi:10.1378/chest.13-2363

Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society clinical practice guidelines for the prevention and treatment of acute altitude illness: 2019 update. Wilderness Environ Med. 2019;30:S3-S18. [PMID: 31248818] doi:10.1016/j.wem.2019.04.006

Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. Eur Respir Rev. 2017;26. [PMID: 28143879] doi:10.1183/16000617.0096-2016

Meier D, Collet TH, Locatelli I, et al. Does this patient have acute mountain sickness?: the Rational Clinical Examination systematic review. JAMA. 2017;318:1810-1819. [PMID: 29136449] doi:10.1001/jama.2017.16192

Nicholson TT, Sznajder JI. Fitness to fly in patients with lung disease. Ann Am Thorac Soc. 2014;11:1614-22. [PMID: 25393882] doi:10.1513/AnnalsATS.201406-234PS

West JB. Physiological effects of chronic hypoxia. N Engl J Med. 2017;376:1965-1971. [PMID: 28514605] doi:10.1056/NEJMra1612008

Critical Care Medicine: ICU Utilization

Hall KK, Lim A, Gale B. The use of rapid response teams to reduce failure to rescue events: A systematic review. J Patient Saf. 2020;16:S3-S7. [PMID: 32809994] doi:10.1097/PTS.0000000000000748

Nates JL, Nunnally M, Kleinpell R, et al. ICU admission, discharge, and triage guidelines: A framework to enhance clinical operations, development of institutional policies, and further research. Crit Care Med. 2016;44:1553-602. [PMID: 27428118] doi:10.1097/CCM.0000000000001856

Zampieri FG, Salluh JIF, Azevedo LCP, et al; ORCHESTRA Study Investigators. ICU staffing feature phenotypes and their relationship with patients' outcomes: an unsupervised machine learning analysis. Intensive Care Med. 2019;45:1599-1607. [PMID: 31595349] doi:10.1007/s00134-019-05790-z

Principles of Critical Care

Brown SM, Bose S, Banner-Goodspeed V, et al; Addressing Post Intensive Care Syndrome 01 (APICS-01) study team. Approaches to addressing post-intensive care syndrome among intensive care unit survivors. A narrative review. Ann Am Thorac Soc. 2019;16:947-956. [PMID: 31162935] doi:10.1513/AnnalsATS.201812-913FR

Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46:e825-e873. [PMID: 30113379] doi:10.1097/CCM.0000000000003299

Girard TD, Alhazzani W, Kress JP, et al; ATS/CHEST Ad Hoc Committee on Liberation from Mechanical Ventilation in Adults. An official American Thoracic Society/American College of Chest Physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Respir Crit Care Med. 2017;195:120-133. [PMID: 27762595] doi:10.1164/rccm.201610-2075ST

Neufeld KJ, Needham DM, Oh ES, et al. Antipsychotics for the prevention and treatment of delirium. Comparative Effectiveness Review No. 219. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2015-00006-I-2.) AHRQ Publication No. 19-EHC019-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2019. doi:10.23970/AHRQEPCCER219

Ouellette DR, Patel S, Girard TD, et al. Liberation from mechanical ventilation in critically ill adults: An official American College of Chest Physicians/American Thoracic Society clinical practice guideline: inspiratory pressure augmentation during spontaneous breathing trials, orotocols minimizing sedation, and noninvasive ventilation immediately after extubation. Chest. 2017;151:166-180. [PMID: 27818331] doi:10.1016/j.chest.2016.10.036

Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50. [PMID: 28860265] doi:10.1183/13993003.02426-2016

Rochwerg B, Einav S, Chaudhuri D, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. Intensive Care Med. 2020;46:2226-2237. [PMID: 33201321] doi:10.1007/s00134-020-06312-y

Taylor BE, McClave SA, Martindale RG, et al; Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med. 2016;44:390-438. [PMID: 26771786] doi:10.1097/CCM.0000000000001525

Thille AW, Muller G, Gacouin A, et al; HIGH-WEAN Study Group and the REVA Research Network. Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: A randomized clinical trial. JAMA. 2019;322:1465-1475. [PMID: 31577036] doi:10.1001/jama.2019.14901

Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. BMJ. 2020;368:l6722. [PMID: 31907223] doi:10.1136/bmj.l6722

Zorowitz RD. ICU-acquired weakness: a rehabilitation perspective of diagnosis, treatment, and functional management. Chest. 2016;150:966-971. [PMID: 27312737] doi:10.1016/j.chest.2016.06.006

Common ICU Conditions

Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al; Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. JAMA. 2017;318:1335-1345. [PMID: 28973363] doi:10.1001/jama.2017.14171

Fan E, Del Sorbo L, Goligher EC, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195:1253-1263. [PMID: 28459336] doi:10.1164/rccm.201703-0548ST

Global Initiative for Asthma. Global strategy for asthma management and prevention, 2021. Accessed May 5, 2021. https://ginasthma.org/gina-reports/

Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report. Accessed September 27, 2020. https://goldcopd.org/gold-reports/

Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update [Editorial]. Intensive Care Med. 2018;44:925-928. [PMID: 29675566] doi:10.1007/s00134-018-5085-0

Moss M, Huang DT, Brower RG, et al; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med. 2019;380:1997-2008. [PMID: 31112383] doi:10.1056/NEJMoa1901686

Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486-552. [PMID: 28098591] doi:10.1097/CCM.0000000000002255

Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10. [PMID: 26903338] doi:10.1001/jama.2016.0287

Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48-79. [PMID: 30348463] doi:10.1016/j.clnu.2018.08.037

Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562-572. [PMID: 28792873] doi:10.1056/NEJMra1608077

Specific Critical Care Topics

Elmer J, Callaway CW. The brain after cardiac arrest. Semin Neurol. 2017;37:19-24. [PMID: 28147414] doi:10.1055/s-0036-1597833

Epstein Y, Yanovich R. Heatstroke. N Engl J Med. 2019;380:2449-2459. [PMID: 31216400] doi:10.1056/NEJMra1810762

Henretig FM, Kirk MA, McKay CA Jr. Hazardous chemical emergencies and poisonings. N Engl J Med. 2019;380:1638-1655. [PMID: 31018070] doi:10.1056/NEJMra1504690

LoVerde D, Files DC, Krishnaswamy G. Angioedema. Crit Care Med. 2017;45:725-735. [PMID: 28291095] doi:10.1097/CCM.0000000000002281

Modi S, Dharaiya D, Schultz L, et al. Neuroleptic malignant syndrome: complications, outcomes, and mortality. Neurocrit Care. 2016;24:97-103. [PMID: 26223336] doi:10.1007/s12028-015-0162-5

Ng PCY, Long BJ, Davis WT, et al. Toxic alcohol diagnosis and management: an emergency medicine review. Intern Emerg Med. 2018;13:375-383. [PMID: 29427181] doi:10.1007/s11739-018-1799-9

Rothberg DL, Makarewich CA. Fat embolism and fat embolism syndrome. J Am Acad Orthop Surg. 2019;27:e346-e355. [PMID: 30958807] doi:10.5435/JAAOS-D-17-00571

Shaker MS, Wallace DV, Golden DBK, et al; Collaborators. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145:1802-1123. [PMID: 32001253]

Vasquez DN, Plante L, Basualdo MN, et al. Obstetric disorders in the ICU. Semin Respir Crit Care Med. 2017;38:218-234. [PMID: 28561253] doi:10.1055/s-0037-1600910

Pulmonary and Critical Care Medicine Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American College of Physicians designates MKSAP 19 Pulmonary and Critical Care Medicine for a maximum of 25.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 25.75 medical knowledge MOC points in the American Board of Internal Medicine's Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

Earn Credits or MOC Points Online

To earn CME credits or to apply for MOC points, MKSAP users need to answer at least one of two questions correctly (earning a score of at least 50%) and click the Submit CME button. Each single MKSAP 19 self-assessment question qualifies for one quarter of a CME credit hour or ABIM MOC point.

MKSAP 19 Subscribers can enter their self-assessment question answers and submit for CME/MOC in two ways:

1. Users of MKSAP 19 Complete who prefer to use their print books and a paper answer sheet to study and record their answers can use the printed answer sheet at the back of this book to record their answers. The corresponding online answer sheets, which are available on the MKSAP 19 Resource Page, may be used to transcribe answers onto the online answer sheets. Users may then submit their answers to qualify for CME credits or MOC points (see below for information on Opting in for MOC). Users who prefer to record their answers on a paper answer sheet should save their answer sheet for future use. Users who study with MKSAP 19 print can also submit their answers directly within MKSAP 19 Digital by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions.

2. Users of MKSAP 19 Digital can enter their answers within the digital program by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions and clicking the Submit CME button once they qualify for CME and are ready to submit. Learners should keep in mind their yearly CME and MOC deadlines when determining the appropriate time to submit.

Learners' CME/MOC submission progress will be shown on the MKSAP 19 Digital CME/MOC/CPD page.

Opting in for MOC

MKSAP 19 users can opt in for simultaneous submission of CME and MOC points as they answer self-assessment questions. To opt in, users will be required to complete a form requesting their name, date of birth, and ABIM number. The MOC Opt-in Form will be presented upon the user's first CME submission and needs to be completed only once.

Directions

Each of the numbered items is followed by lettered answers. Select the ***ONE*** *lettered answer that is* ***BEST*** *in each case.*

Item 1

An 87-year-old woman was hospitalized 2 days ago for sepsis related to pyelonephritis. Medical history is significant for hypertension and heart failure. She has responded to fluid resuscitation and antibiotic therapy but is intermittently confused. She reports no pain. Attempts have been made not to interrupt her night-time sleep. Nurses provide frequent orientation, and she has been provided with her glasses and hearing aids. Medications are ceftriaxone, acetaminophen, carvedilol, hydrochlorothiazide, and lisinopril.

On physical examination, vital signs are normal. Oxygen saturation is 92% breathing oxygen, 2 L/min by nasal cannula. She is awake and oriented. There are no focal neurologic deficits.

Which of the following is the most appropriate measure to prevent delirium?

(A) Early mobilization
(B) Haloperidol
(C) Lorazepam
(D) Melatonin

Item 2

A 42-year-old man is evaluated at a follow-up appointment. He underwent polysomnography 6 weeks ago because of suspected obstructive sleep apnea. The study showed moderate obstructive sleep apnea (apnea-hypopnea index 20) that was controlled with continuous positive airway pressure (CPAP). Although daytime alertness has improved with CPAP, the apparatus is cumbersome to transport on his frequent business trips. At his last visit, the physical examination was normal except for a BMI of 34.

The patient is enrolled in a supervised weight loss program and has started to exercise.

Which of the following is the most appropriate treatment?

(A) Hypoglossal nerve stimulator
(B) Maxillomandibular advancement surgery
(C) Oral appliance
(D) Uvulopalatopharyngoplasty

Item 3

A 25-year-old man is evaluated in the emergency department for worsening shortness of breath and right-side pleuritic chest pain, which developed 1 hour ago. He has an 8-pack-year history of smoking cigarettes. His medical history is otherwise unremarkable, including the absence of lung disease. He is a professional scuba diver.

On physical examination, blood pressure is 150/70 mm Hg, pulse rate is 105/min, and respiration rate is 30/min. Oxygen saturation is 92% with the patient breathing ambient air. There are decreased breath sounds, reduced expansion, and hyperresonance to percussion on the right side.

Chest radiograph reveals a large right pneumothorax and no signs of tension.

Smoking cessation counseling and an offer of varenicline are planned at the time of discharge.

Which of the following is the most appropriate additional pneumothorax management?

(A) Catheter thoracostomy followed by pleurodesis
(B) Needle aspiration
(C) Observation
(D) Supplemental oxygen and observation

Item 4

A 72-year-old man is evaluated in the emergency department for decreasing responsiveness after he spent the day at the zoo. The outside temperature was 38.9 °C (102.0 °F). He also has hypertension. Medications are hydrochlorothiazide and lisinopril.

On physical examination, temperature is 40.5 °C (104.9 °F), blood pressure is 97/54 mm Hg, pulse rate is 117/min, respiration rate is 22/min, and oxygen saturation is 96% with the patient breathing ambient air. He is somnolent. His skin is flushed, warm, and dry. Other than tachycardia, cardiac and pulmonary examinations are normal.

Laboratory results are pending.

Which of the following is the most appropriate treatment?

(A) Acetaminophen
(B) Dantrolene
(C) Evaporative cooling
(D) Immersion in ice water

Item 5

A 67-year-old man is evaluated for progressive shortness of breath and dry cough over the past 3 months. He has a 40-pack-year history of cigarette smoking. His only medication is an albuterol inhaler.

On physical examination, pulse rate is 90/min and respiration rate is 24/min. Oxygen saturation is 88% with the patient breathing ambient air. Auscultation demonstrates bibasilar crackles. Clubbing is present.

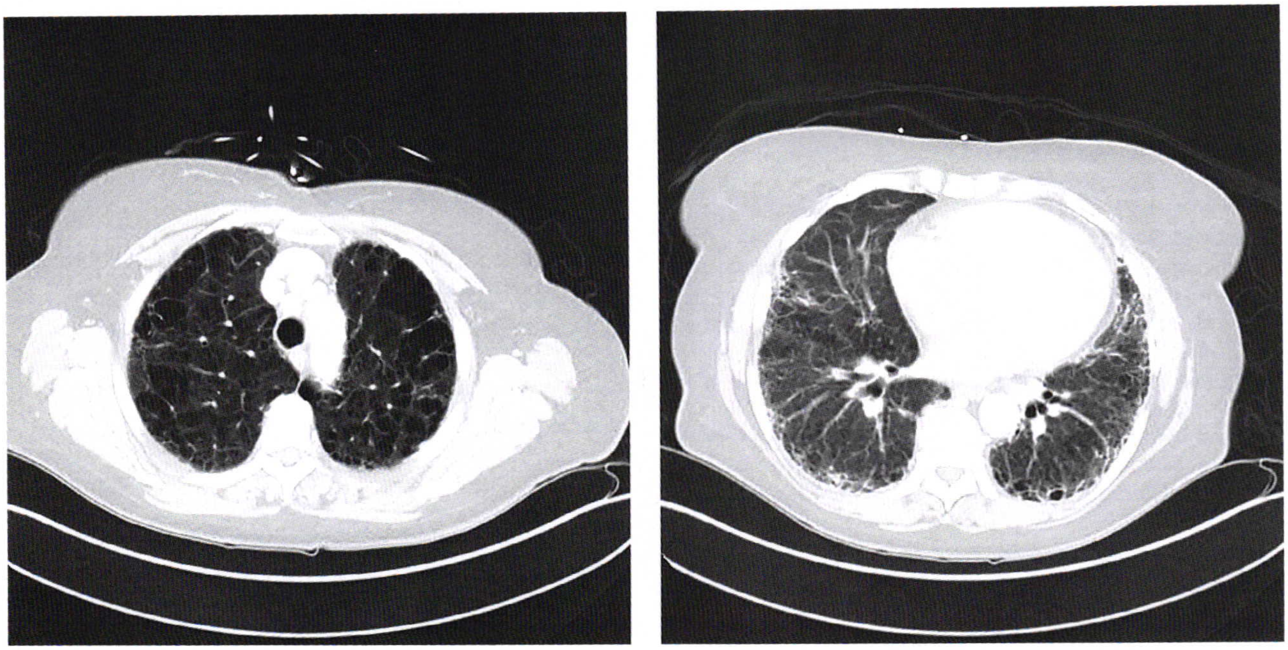
Spirometry shows an FVC of 110% of predicted, an FEV_1 of 95% of predicted, an FEV_1/FVC ratio of 0.68, and a DLCO of 36% of predicted.

An echocardiogram shows normal left ventricle ejection fraction. Right ventricle systolic pressure is 66 mm Hg.

Representative high-resolution CT chest images are shown (top of next page).

Which of the following is the most likely diagnosis?

(A) Acute interstitial pneumonia
(B) Combined pulmonary fibrosis and emphysema
(C) Desquamative interstitial pneumonia
(D) Idiopathic pulmonary fibrosis



ITEM 5

Item 6

A 36-year-old woman is evaluated for a change in her asthma status. She has spirometry-confirmed asthma; she has never required hospitalization. She is a nonsmoker and has allergic rhinitis. Her only medication is an albuterol metered-dose inhaler as needed. She now requires albuterol use three times weekly but never more than once per day. She demonstrates good inhaler technique.

On physical examination, vital signs are normal. Oxygen saturation is 98% with the patient breathing ambient air. BMI is 24. She is not currently wheezing. The remainder of the examination is normal.

Spirometry today is normal.

Which of the following is the most appropriate management?

- (A) Beclomethasone dipropionate with albuterol
- (B) Methacholine challenge testing
- (C) Montelukast at bedtime
- (D) No additional management

Item 7

A 53-year-old woman presents for follow-up evaluation of an incidentally found 4-mm solid lung nodule in the right lower lobe on abdominal CT scan. The CT scan showed no other nodules, no lymphadenopathy, and unremarkable lung parenchyma. There are no old scans for comparison. She has no personal or family history of lung cancer.

She is asymptomatic, a lifelong nonsmoker, and has no significant exposure history.

Which of the following is the most appropriate management?

- (A) Bronchoscopy with lung biopsy
- (B) CT of chest in 12 months
- (C) CT-guided lung biopsy
- (D) Fluorodeoxyglucose PET
- (E) No further follow-up

Item 8

A 59-year-old man is seen in a follow-up visit for a 6-month history of progressively worsening chronic cough productive of small amounts of thin clear sputum and dyspnea on exertion. He has shortness of breath when he walks quickly and when he walks uphill. He has a 45-pack-year smoking history but quit 2 years ago. He has been using albuterol as needed since his diagnosis of COPD 3 months ago, but he remains symptomatic.

On physical examination, oxygen saturation is 95% with the patient breathing ambient air. Scattered expiratory wheezing is heard. Cardiac examination is normal.

Chest radiograph from 3 months ago shows flattened diaphragm but no infiltrate.

Spirometry at the time of diagnosis showed reduced postbronchodilator FEV_1/FVC ratio and FEV_1 of 69% of predicted.

Which of the following is the most appropriate pharmacologic treatment?

- (A) Inhaled fluticasone propionate–salmeterol
- (B) Inhaled tiotropium bromide
- (C) Prednisone
- (D) Roflumilast

Item 9

H

A 35-year-old man is evaluated in the emergency department 4 hours after being rescued from his burning home by firefighters. He initially refused transportation to the

CONT.

hospital but now desires an evaluation. He reports tracheal irritation with breathing, sore throat, and a change in his voice.

On physical examination, he is alert and in moderate pain. Temperature is 37.5 °C (99.5 °F), blood pressure is 144/90 mm Hg, pulse rate is 100/min, and respiration rate is 26/min. Oxygen saturation is 96% with the patient breathing ambient air. He has dysphonia. There is no soot in the nares or the oral pharynx or burns on his face, neck, or thorax. Nonobstructing edema of the oropharynx is noted. Cardiac examination reveals a regular rhythm. Chest is clear to auscultation; there is no stridor.

Arterial blood gas studies:

pH	7.45
Pco$_2$	35 mm Hg (4.7 kPa)
Po$_2$	95 mm Hg (12.6 kPa)

A chest radiograph shows no infiltrates.

Which of the following is the most appropriate management?

(A) Bronchoscopy
(B) Methylprednisolone
(C) Nebulized epinephrine
(D) Noninvasive positive pressure ventilation

Item 10

A 42-year-old man is evaluated for fatigue, dyspnea, and lightheadedness. He was diagnosed with a provoked pulmonary embolism 5 months ago and has been taking apixaban since then. Initially, his dyspnea and tachycardia improved, but over the past 2 months, he has had progressive exertional dyspnea.

On physical examination, vital signs are normal. BMI is 28. Cardiopulmonary examination is normal.

An echocardiogram reveals right atrial enlargement and right ventricular hypertrophy and an elevated mean pulmonary artery pressure.

Which of the following is the most appropriate diagnostic test?

(A) CT angiography of the chest
(B) D-dimer assay
(C) Right heart catheterization and pulmonary angiography
(D) Ventilation/perfusion scan

Item 11

A 59-year-old woman was hospitalized for a first COPD exacerbation 5 days ago and is now preparing for discharge. She quit smoking 5 years ago. Immunizations are up to date. Medications are daily tiotropium bromide and albuterol inhalers as needed. Prednisone is to be discontinued today.

On physical examination, vital signs are normal. Oxygen saturation at rest is 87% with the patient breathing ambient air. Breath sounds are distant, without wheezing. Cardiovascular examination is normal.

Complete blood count is normal.

Arterial blood gas studies (at time of discharge):

pH	7.42
Pco$_2$	44 mm Hg (5.8 kPa)
Po$_2$	55 mm Hg (7.3 kPa)

Which of the following is the most appropriate additional treatment?

(A) Aminophylline
(B) Home oxygen
(C) Noninvasive positive pressure ventilation
(D) Stop current inhalers; start inhaled fluticasone

Item 12

A 74-year-old man is evaluated in the ICU for sepsis and hypotension. A central venous catheter has just been inserted into the left internal jugular vein under ultrasound visualization to start vasopressor therapy. As the catheter line is being secured, the patient suddenly becomes more hypotensive. Medications are propofol, piperacillin-tazobactam, and vancomycin.

Temperature is 37.8 °C (100.0 °F), blood pressure is 74/55 mm Hg, pulse rate is 118/min, and respiration rate is 18/min on mechanical ventilation. Oxygen saturation is 91% on Fio$_2$ of 1.00. Breath sounds are diminished bilaterally. Heart sounds are diminished.

Which of the following is the most appropriate next management step?

(A) Chest CT
(B) Chest ultrasonography
(C) Needle thoracostomy
(D) Removal of central venous catheter

Item 13

A 35-year-old woman is evaluated for a cough and wheezing occurring several times during the week, unrelated to exercise. She has a history of asthma that was previously well controlled with a budesonide inhaler. She is also taking albuterol five times weekly with good response. Her symptoms have woken her once in the past month. She reports no additional symptoms and no environmental triggers. She is a nonsmoker. Inhaler technique is good.

On physical examination, vital signs are normal. Oxygen saturation is 96% with the patient breathing ambient air. Expiratory wheezing is noted.

Which of the following treatments should be started?

(A) Add formoterol
(B) Azithromycin
(C) Prednisone
(D) Tiotropium

Item 14

A 57-year-old woman is evaluated at a follow-up visit after discharge from the hospital for a COPD exacerbation. This was her third hospitalization for a COPD exacerbation in the past 6 months. She no longer smokes cigarettes. Medications are fluticasone-umeclidinium-vilanterol and albuterol inhalers. She has been adherent with her medication, has excellent inhaler technique, and continues to use home oxygen. Between exacerbations she has a cough productive of thin, colorless sputum.

On physical examination, vital signs are normal. Oxygen saturation is 93% breathing oxygen, 2 L/min by nasal cannula. Scattered expiratory wheezing is heard. Cardiac examination is normal.

Spirometry shows postbronchodilator reduced FEV_1/FVC ratio and an FEV_1 of 45% of predicted.

Influenza, COVID-19, and pneumococcal pneumonia vaccinations are brought up to date. The patient is enrolled in a pulmonary rehabilitation program. α_1-Antitrypsin level is normal.

Which of the following additional long-term treatments is most appropriate?

(A) α_1-Antitrypsin augmentation therapy
(B) Azithromycin
(C) Metoprolol
(D) Oral *N*-acetylcysteine

Item 15

A 63-year-old man is evaluated for dyspnea. The patient has newly diagnosed stage IV lung adenocarcinoma with a right malignant pleural effusion. A thoracentesis removed 1200 mL of bloody fluid 5 days ago with relief of dyspnea. Follow-up chest radiograph documented incomplete expansion of the right lung, with air replacing the removed pleural fluid. He has returned to the emergency department today with increasing dyspnea.

On physical examination, vital signs are normal. Respiration rate is 18/min. Oxygen saturation is 93% with the patient breathing ambient air. Lung examination is consistent with a large right pleural effusion.

Repeat chest radiograph shows a large right-sided pleural effusion with loculations.

Which of the following is the most appropriate management?

(A) Chemical pleurodesis
(B) Indwelling pleural catheter
(C) Repeat thoracentesis
(D) Surgical decortication

Item 16

A 31-year-old man is evaluated following an abnormal finding on a chest radiograph obtained as a part of pre-employment screening. He is a lifelong nonsmoker with no history of dust exposure. His medical history is unremarkable, and he has no known respiratory or constitutional symptoms.

The vital signs and physical examination are normal.

Spirometry is normal.

Chest radiograph reveals bilateral symmetric hilar prominence with clear lung fields.

Interferon-γ release assay is normal.

Which of the following is the most appropriate management?

(A) Bronchoscopic biopsy
(B) Methotrexate
(C) Prednisone
(D) Observation

Item 17

A 40-year-old man is evaluated 10 days after an emergency department visit for a cough, chest tightness, wheezing, and shortness of breath. He was treated with nebulized albuterol and sent home with a 5-day course of prednisone and an albuterol metered-dose inhaler. Since completing the prednisone, he has felt well, with no further symptoms and no need to use the albuterol. He reports a similar episode requiring an emergency department visit 1 year ago.

On physical examination, vital signs are normal. Oxygen saturation is 97% with the patient breathing ambient air. Cardiopulmonary examination is normal.

Spirometry is normal.

Which of the following is the most appropriate management?

(A) Budesonide-salmeterol
(B) Fluticasone
(C) Measurement of exhaled nitric oxide
(D) Methacholine challenge testing

Item 18

A 59-year-old woman is evaluated 5 days after her admission to the hospital for septic shock with no obvious source of infection. She is neutropenic. She has large B-cell lymphoma and received her last course of chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) 5 days before admission. Piperacillin-tazobactam, gentamicin, and vancomycin were initiated. Gentamicin and vancomycin were discontinued 2 days ago following confirmation of negative blood cultures. She is clinically improved and has been afebrile for 24 hours.

On physical examination, temperature is 36.9 °C (98.4 °F); the remainder of the vital signs and physical examination findings are normal.

Laboratory studies show a leukocyte count of 1500/µL (1.5×10^9/L); absolute neutrophil count is 100/µL (0.1×10^9/L).

Which of the following is the most appropriate treatment?

(A) Change to imipenem-cilastatin
(B) Discontinue piperacillin-tazobactam
(C) No change in treatment
(D) Start voriconazole

Item 19

A 49-year-old man is transferred from a psychiatric hospital to the emergency department because of a change in vital signs and encephalopathy. He has schizophrenia and depression. He was hospitalized 3 days ago for acute psychosis and attempted suicide. In the psychiatric hospital, he was treated with risperidone and fluoxetine. He subsequently developed nausea and vomiting and was prescribed promethazine.

On physical examination, temperature is 39.5 °C (103.1 °F), blood pressure is 173/112 mm Hg, pulse rate is 132/min, respiration rate is 26/min, and oxygen saturation is 99% with the patient breathing ambient air. He is diaphoretic and tachypneic, with clear lungs. He has tachycardia without murmur, gallops, or rubs. Muscles are rigid. Deep tendon reflexes are normal.

Promethazine is discontinued.

Which of the following is the most appropriate initial treatment?

(A) Discontinue fluoxetine
(B) Discontinue risperidone
(C) Start cyproheptadine
(D) Start dantrolene

Item 20

A 38-year-old man is evaluated for shortness of breath and a dry cough for the past 3 months. He has a 20-pack-year smoking history and continues to smoke.

On physical examination, vital signs are normal. Oxygen saturation is 92% with the patient breathing ambient air. Auscultation of the lungs reveals coarse bibasilar inspiratory crackles. The cardiac examination and remainder of the physical examination are normal.

Chest radiograph demonstrates bilateral reticular infiltrates. High-resolution chest CT demonstrates patchy ground-glass infiltrates with lower-lobe predominance. Pulmonary function testing shows an FVC of 65% of predicted, an FEV_1/FVC ratio of 0.81, and a DLCO of 56% of predicted.

Which of the following is the most appropriate treatment?

(A) Glucocorticoids
(B) Methotrexate
(C) Pirfenidone
(D) Smoking cessation

Item 21

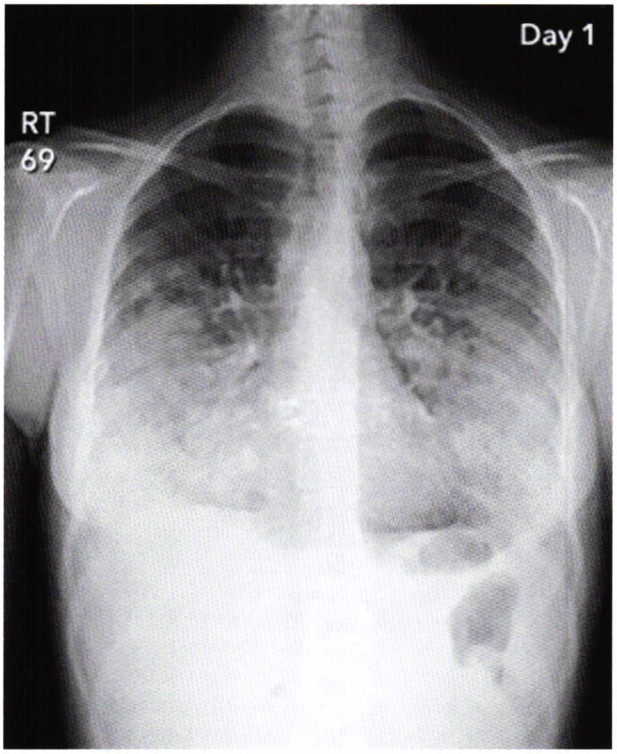
A 36-year-old woman is evaluated for respiratory failure requiring invasive mechanical ventilation following a motor vehicle accident.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 100/65 mm Hg, pulse rate is 100/min, and respiration rate is 26/min. Oxygen saturation is 90% with an FIO_2 of 0.50 and positive end-expiratory pressure of 12 cm H_2O. There are multiple contusions on her chest. Estimated central venous pressure is normal. Other than tachycardia, cardiac examination is normal. There are diffuse lung crackles.

Arterial blood gas studies:

pH	7.3
PCO_2	50 mm Hg (6.6 kPa)
PO_2	66 mm Hg (8.8 kPa)

Chest radiograph is shown.



Hemoglobin has remained stable. Echocardiogram reveals a normal ejection fraction and valvular function. ECG shows only sinus tachycardia.

Which of the following is the most likely diagnosis?

(A) Acute respiratory distress syndrome
(B) Diffuse alveolar hemorrhage
(C) Pulmonary edema
(D) Pulmonary embolism

Item 22

A 28-year-old woman is evaluated for sleepiness and difficulty staying awake over the past 6 months. She works as a hospital respiratory therapist. Half of her shifts are from 7:00 PM to 7:00 AM. The sleepiness subsides by the time she drives home, and she then has difficulty falling asleep during the day. Her sleepiness has slowed her cognitive processing during working hours and has resulted in depressed mood.

On physical examination, blood pressure is 118/68 mm Hg and pulse rate is 76/min. BMI is 24.

Which of the following is the most appropriate management?

(A) Education and counseling
(B) Home sleep apnea testing
(C) Modafinil
(D) Zolpidem

Item 23

A 77-year-old man is evaluated in the hospital for shortness of breath, dry cough, pleuritic chest pain, and unintentional 9-kg (20-lb) weight loss over the past 6 months.

On physical examination, the patient appears chronically ill. Vital signs are normal. BMI is 19. There are decreased breath sounds at the right base.

Chest radiograph demonstrates an apparent pleural effusion on the right side, but CT scan reveals a nodular pleura-based mass on the right side.

Which of the following is the most likely occupational exposure?

(A) Asbestos
(B) Coal
(C) Cobalt
(D) Silica

Item 24

A 50-year-old man is referred for poorly controlled asthma. Triggers include exercise and exposure to dust, pollen, and fumes. He has allergic rhinitis. He has been treated with several courses of glucocorticoids, but symptoms recurred after he stopped treatment despite regular use of his fluticasone-salmeterol and tiotropium inhalers. His only other medication is albuterol. He has good inhaler technique.

On physical examination, vital signs are normal. BMI is 23. Pulmonary examination reveals few expiratory wheezes. The remainder of the examination is unremarkable.

Laboratory studies reveal a normal total IgE level and complete blood count.

Chest radiograph is normal. Spirometry demonstrates moderate airflow obstruction that improves with bronchodilators.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Absolute blood eosinophil count
(B) α_1-Antitrypsin level
(C) *Aspergillus*-specific IgE level
(D) Measurement of common allergen-specific IgE levels

Item 25

A 46-year-old woman is evaluated for cough, shortness of breath, wheezing, and chest tightness of 3 weeks' duration. The patient is a janitor in a hospital, and her symptoms started after she mopped up a spill in the cleaning supplies cabinet. Medical history is otherwise unremarkable.

On physical examination, respiration rate is 20/min. Oxygen saturation is 98% with the patient breathing ambient air. There is diffuse expiratory wheezing over both lung fields.

Spirometry reveals an FVC of 88% of predicted, an FEV$_1$ of 55% of predicted, and an FEV$_1$/FVC ratio of 0.6. Postbronchodilator testing reveals significant bronchodilator responsiveness.

Chest radiograph is normal.

Which of the following is the most appropriate next diagnostic step?

(A) Allergy testing
(B) Bronchoscopy
(C) Methacholine challenge test
(D) Review Safety Data Sheet

Item 26

A 66-year-old man is evaluated for a 7-month history of gradually progressive shortness of breath and dry cough. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Oxygen saturation is 93% with the patient breathing ambient air. Auscultation reveals fine end-inspiratory bibasilar crackles. Clubbing is present. There are no rashes or edema. Cardiac examination is unremarkable.

Chest radiograph reveals small lung volumes and bibasilar reticular infiltrates without lymphadenopathy. Spirometry reveals an FEV$_1$/FVC ratio of 0.87, an FVC of 62% of predicted, and a DLCO of 48% of predicted.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bronchoscopic lung biopsy
(B) Cardiopulmonary exercise test
(C) Chest CT angiography
(D) High-resolution chest CT
(E) Transthoracic echocardiography

Item 27

A 24-year-old woman is evaluated in the emergency department for acute onset of dyspnea and pleuritic chest pain. She is 10 weeks pregnant. She is otherwise well, and her only medication is folic acid.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 140/78 mm Hg, pulse rate is 90/min, respiration rate is 24/min, and oxygen saturation is 95% with the patient breathing ambient air. Cardiopulmonary examination is normal. There is no evidence of deep venous thrombosis.

A chest radiograph is normal. A ventilation/perfusion lung scan is interpreted as high probability for pulmonary embolism.

Which of the following is the most appropriate treatment?

(A) Dabigatran
(B) Fondaparinux
(C) Low-molecular-weight heparin
(D) Rivaroxaban
(E) Unfractionated heparin followed by warfarin

Item 28

A 77-year-old man is evaluated for acute agitation with worsening of oxygenation, hypotension, and tachycardia over the last 30 minutes. He was hospitalized 2 days ago with pneumonia and hypoxemic respiratory failure requiring mechanical ventilation. Medical history is also significant for COPD and heart failure. Medications are cefotaxime, levofloxacin, propofol, furosemide, albuterol, and low-molecular-weight heparin.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 102/55 mm Hg, pulse rate is 122/min, and respiration rate is 30/min. Oxygen saturation is 87% with a tidal volume of 420 mL, a positive end-expiratory pressure of 8 cm H_2O, and $\mathrm{FIO_2}$ of 0.50. Trachea is midline. Pulmonary examination reveals decreased breath sounds bilaterally. The jugular vein is difficult to visualize; an S_3 is present.

Which of the following is the most appropriate management?

(A) Bedside thoracic ultrasonography
(B) CT of the chest
(C) Infusion of cisatracurium
(D) Needle thoracostomy

Item 29

A 62-year-old woman is evaluated in the emergency department for fatigue, headaches, confusion, and weakness that have progressed over the past 6 weeks. She has an 11.3 kg (25 lb) unintentional weight loss over the past month. She has an 85-pack-year history of smoking and quit smoking 3 months ago.

On physical examination, blood pressure is 125/75 mm Hg, pulse rate is 92/min, respiration rate is 21/min, and oxygen saturation is 89% with the patient breathing ambient air. BMI is 17. An expiratory wheeze is noted on the left side. The remainder of the examination is normal.

Laboratory evaluation reveals a serum sodium level of 123 mEq/L (123 mmol/L).

CT scan of the chest shows a 4-cm mediastinal mass compressing the left upper lobe bronchus with associated bulky mediastinal lymphadenopathy.

Which of the following is the most likely diagnosis?

(A) Adenocarcinoma of lung
(B) Fibrosing mediastinitis
(C) Large cell lung cancer
(D) Small cell lung cancer

Item 30

A 69-year-old man is evaluated for shortness of breath and a dry cough progressing over the past 7 months. His medical history is otherwise unremarkable, and he does not take any medications.

On physical examination, respiration rate is 25/min. Oxygen saturation is 94% with the patient breathing ambient air. Auscultation of the lungs reveals Velcro-like crackles at both lung bases. Cardiac examination is normal.

Laboratory test results, including serologic tests for connective tissue disease, are negative.

Pulmonary function testing reveals a restrictive pattern and a DLCO of 42% of predicted.

Chest radiograph reveals reticular infiltrates in the lower lung zones. High-resolution chest CT scan findings are consistent with a usual interstitial pneumonia pattern.

Which of the following is the most appropriate treatment?

(A) *N*-acetylcysteine
(B) Pirfenidone
(C) Prednisone, *N*-acetylcysteine, and azathioprine
(D) Warfarin

Item 31

A 50-year-old woman was admitted to the ICU 24 hours ago for management of acute respiratory distress syndrome due to pneumonia. She is on a mechanical ventilator. She is receiving vasopressors for hypotension. Medications are norepinephrine, fentanyl drip, and propofol drip.

On physical examination, vital signs are stable. Oxygen saturation is 90%, with an $\mathrm{FIO_2}$ of 0.60, and positive end-expiratory pressure is 12 cm H_2O. The patient is deeply sedated and unresponsive to physical stimulation.

Which of the following is the most appropriate management?

(A) Downward titration of sedation medication
(B) Electroencephalography
(C) Head CT
(D) Hold sedation and analgesia

Item 32

A 45-year-old woman is evaluated for increasing shortness of breath and fatigue for the past 6 weeks and weight loss of 4.5 kg (10 lb) over the past 2 months. She has no other symptoms. She has a history of rheumatoid arthritis. Her only medications are methotrexate and folic acid.

On physical examination, vital signs are normal. Typical chronic changes of rheumatoid arthritis are present in her hands, wrists, and feet in the absence of active synovitis. Chest findings are consistent with bilateral pleural effusions.

Complete blood count is normal. Serum lactate dehydrogenase level is 200 U/L, and total serum protein level is 6 g/dL (60 g/L).

H CONT.

Pleural fluid studies:

Leukocytes	600/µL (0.6×10^9/L) (70% lymphocytes)
pH	7.4
Glucose	100 mg/dL (5.5 mmol/L)
Lactate dehydrogenase	85 U/L
Total protein	4.1 gm/dL (41 g/L)
Total cholesterol	120 mg/dL (3.1 mmol/L)
Triglycerides	140 mg/dL (1.58 mmol/L)

Chest radiograph demonstrates bilateral pleural effusions and bulky mediastinal lymphadenopathy. Thoracentesis is performed, and 1100 mL of milky fluid is drained.

Which of the following is the most likely diagnosis?

(A) Cholesterol effusion
(B) Chylothorax
(C) Empyema
(D) Rheumatoid effusion

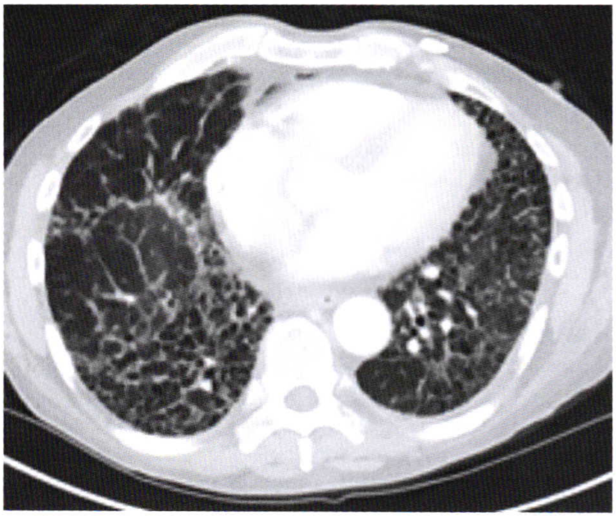
Item 33

A 66-year-old man is evaluated for gradually progressive dyspnea and dry cough over the past 6 months. He has a 30-pack-year history of smoking; he stopped 10 years ago. Medical history is otherwise unremarkable.

On physical examination, respiration rate is 22/min. Oxygen saturation is 93% with the patient breathing ambient air. Auscultation of the lungs reveals fine end-inspiratory Velcro-like crackles at both lung bases. Clubbing is present.

Spirometry shows an FVC of 55% of predicted, an FEV_1/FVC ratio of 0.91, and a DLCO of 42% of predicted.

A high-resolution CT scan of the chest is shown.



Which of the following is the most likely diagnosis?

(A) Cryptogenic organizing pneumonia
(B) Idiopathic pulmonary fibrosis
(C) Nonspecific interstitial pneumonia
(D) Respiratory bronchiolitis-associated interstitial lung disease

Item 34

H

A 37-year-old woman is evaluated in the emergency department for headache, dyspnea, and cough. Two days ago she traveled from her home at 300 meters (984 feet) above sea level to a mountain ski resort where the slopes are as high as 3914 meters (12,841 feet). She developed the headache yesterday, and today it is worse and she has shortness of breath and a cough.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 124/72 mm Hg, pulse rate is 115/min, and respiration rate is 28/min. Oxygen saturation is 82% with the patient breathing ambient air. Inspiratory crackles are present bilaterally.

Chest radiograph demonstrates patchy alveolar infiltrates.

High-flow supplemental oxygen by nasal cannula is initiated.

Which of the following is the most appropriate additional treatment?

(A) Acetazolamide, orally
(B) Ceftriaxone, intravenously
(C) Descent to a lower altitude
(D) Dexamethasone, orally
(E) Furosemide, intravenously

Item 35

H

An 84-year-old man living in a nursing home is evaluated in the emergency department for recent onset of unresponsiveness and fever. He has Alzheimer dementia.

On physical examination, temperature is 39.3 °C (102.7 °F), blood pressure is 88/50 mm Hg, pulse rate is 106/min, and respiration rate is 18/min. Oxygen saturation is 95% with the patient breathing ambient air. The patient is responsive only to physical stimuli. Cardiopulmonary examination reveals normal heart and lung sounds. Abdominal examination is normal. A 6 × 6 cm necrotic sacral decubitus wound is present.

Laboratory data are pending. Blood cultures are obtained.

Which of the following is the most appropriate resuscitative treatment?

(A) 5% albumin solution
(B) 150 mEq bicarbonate in 5% dextrose
(C) Hydroxyethyl starch
(D) Lactated Ringer solution

Item 36

A 63-year-old woman is evaluated at a follow-up visit for a solitary pulmonary nodule. Six months ago CT angiography (CTA) was performed to evaluate a possible pulmonary embolism. The CTA was negative but demonstrated an 8-mm ground-glass (subsolid) nodule in the left upper lobe. The patient has a 21-pack-year history of cigarette smoking but stopped 6 months ago. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs and other examination findings are normal.

A repeat chest CT scan 6 months after the initial scan shows no change in the size or characteristics of the nodule.

Which of the following is the most appropriate management?

(A) Chest CT every 2 years for 5 years
(B) Chest CT in 12 months
(C) Fluorodeoxyglucose PET
(D) Surgical resection

Item 37

A 57-year-old woman is evaluated for a 4-month history of progressive exertional dyspnea and occasional chest pain and palpitations. She has limited cutaneous systemic sclerosis with Raynaud phenomenon and gastroesophageal reflux disease. Medications are omeprazole and diltiazem.

On physical examination, blood pressure is 107/74 mm Hg and pulse rate is 90/min. Oxygen saturation is normal at rest. Characteristic skin findings of limited cutaneous systemic sclerosis are present. New cardiac findings include jugular venous distention, persistent splitting of S_2, and 2/6 systolic murmur at the left lower sternal border that increases with inspiration. Lungs are clear.

ECG shows a heart rate of 95/min and is otherwise normal. Chest radiograph is normal. Echocardiography performed 12 months ago was normal.

Which of the following is the most appropriate diagnostic test?

(A) CT angiography of the chest
(B) Echocardiography
(C) Exercise stress test
(D) Pulmonary function testing

Item 38

A 52-year-old man is evaluated following a diagnosis of severe obstructive sleep apnea 8 weeks ago. He was prescribed auto-adjusting positive airway pressure therapy. He uses a nasal mask with heated humidification. He still feels drowsy during the day.

Which of the following is the most appropriate management?

(A) Assess adherence
(B) Bilevel positive airway pressure ventilation
(C) Eszopiclone
(D) Modafinil

Item 39

An 81-year-old man is evaluated in the hospital for pneumonia.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 119/65 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. Oxygen saturation is 88% with the patient breathing ambient air. There are coarse rhonchi and decreased breath sounds and dullness to percussion over the left lower half of the chest.

CT scan of the chest shows left lower lobe consolidation and loculated left pleural effusion. A thoracentesis is performed.

Which of the following pleural fluid tests is most appropriate in directing therapy?

(A) Lactate dehydrogenase
(B) pH
(C) Procalcitonin
(D) Total protein

Item 40

A 27-year-old woman is evaluated for a cough and chest tightness that occur during and after exercise. She has been training for her first marathon, but she has been unable to increase her training intensity because of these symptoms. She denies cough or chest tightness at any other time. She reports no stridor, throat tightness, or noisy inspiration during the episodes.

On physical examination, vital signs and pulmonary examination are normal.

Baseline spirometry is normal. Exercise testing demonstrates a significant decrease in FEV_1 from baseline.

Which of the following inhaled medications is the most appropriate next step in treatment?

(A) Salmeterol daily
(B) Budesonide twice daily
(C) Budesonide-formoterol before exercise
(D) Ipratropium before exercise

Item 41

A 27-year-old woman is evaluated in the emergency department for difficulty breathing following a hornet sting to the leg.

On physical examination, blood pressure is 86/54 mm Hg, pulse rate is 130/min, and respiration rate is 20/min. Expiratory wheezing is noted. Her lips are swollen. Urticarial skin lesions are present.

She is administered 1 L of intravenous 0.9% saline, nebulized albuterol, and intramuscular epinephrine. Vital signs normalize, and dyspnea improves. Forty-five minutes later, systolic blood pressure is 90 mm Hg, pulse rate is 128/min, and wheezing has returned.

Which of the following is the most appropriate treatment?

(A) Diphenhydramine
(B) Epinephrine
(C) Famotidine
(D) Methylprednisolone
(E) Norepinephrine

Item 42

A 32-year-old man is evaluated in the emergency department after being found unresponsive at home. Methadone and lorazepam pill bottles were found nearby. At the scene, respiratory rate was 6/min. He was administered supplemental oxygen and intranasal naloxone, followed by intravenous naloxone. Food found in his mouth was cleared.

In the emergency department, intravenous naloxone is repeated. Temperature is 37.2 °C (99.0 °F), blood pressure is 120/68 mm Hg, pulse rate is 80/min, respiratory rate is 10/min, and oxygen saturation is 90% breathing oxygen, 5 L/min by nasal cannula. The patient is unresponsive. Pupillary miosis is present but responsive to light.

The fingerstick blood glucose level is 88 mg/dL (4.9 mmol/L).

Portable chest radiograph shows a right lower lobe infiltrate.

Which of the following is the most appropriate treatment?

(A) Endotracheal intubation
(B) Flumazenil
(C) Intravenous naloxone infusion
(D) Oxygen by nonrebreather mask

Item 43

A 23-year-old man is evaluated for cough, rhinorrhea, and wheezing of 3 weeks' duration. He has no fevers, chills, or chest pain and no history of asthma or allergies. He is a pastry chef and notes that his symptoms improve on nonworking weekends.

On physical examination, vital signs are normal. Oxygen saturation is 94% with the patient breathing ambient air. Expiratory wheezing is noted.

Laboratory studies show a normal *Aspergillus*-specific IgE level.

Spirometry reveals moderate airflow obstruction that improves after inhaled albuterol.

Chest radiograph is normal.

Which of the following is the most likely diagnosis?

(A) Acute bronchitis
(B) Acute hypersensitivity pneumonitis
(C) Allergic bronchopulmonary aspergillosis
(D) Occupational asthma

Item 44

A 62-year-old man is evaluated in follow-up examination for COPD. Despite smoking cessation, adherence to his medical regimen, good inhaler technique, and participation in pulmonary rehabilitation, he continues to experience breathlessness with mild exertion and has diminished quality of life. He has a minimal dry cough, and he has never required treatment for an acute exacerbation of COPD. Medications are fluticasone-umeclidinium-vilanterol and albuterol inhalers as needed. Immunizations are up to date.

On physical examination, vital signs are normal. Oxygen saturation is 93% with the patient breathing ambient air. There are diminished breath sounds.

A 6-minute walk test shows a minimum oxygen saturation of 90% with the patient breathing ambient air. Spirometry shows an FEV_1 of 35% of predicted and a DLCO of 42% of predicted.

Chest imaging shows upper-lobe-predominant emphysema.

Which of the following is the most appropriate treatment?

(A) Long-term azithromycin therapy
(B) Lung volume reduction surgery
(C) Roflumilast
(D) Supplemental oxygen

Item 45

A 48-year-old man is evaluated in the emergency department for an acute myocardial infarction. Medical history is significant for hyperlipidemia. His only medication is atorvastatin.

On physical examination, pulse rate is 56/min. Other vital signs are normal. Oxygen saturation is 96% with the patient breathing ambient air. Cardiac examination reveals an S_4. Lungs are clear.

The initial serum troponin I level is elevated. An ECG shows ST-segment elevations in leads II, III, and aVF. A chest radiograph is normal.

Which of the following is the most appropriate oxygen management?

(A) Oxygen by nonrebreather mask
(B) Oxygen by Venturi mask
(C) Oxygen, 3 L/min by nasal cannula
(D) No additional oxygen management

Item 46

A 52-year-old man is evaluated after hospital discharge for total knee arthroplasty. In the recovery room following the procedure, he was reintubated because of hypoxemia, which was then completely resolved. The postintubation chest radiograph was normal. Hypoxemia did not return following extubation 24 hours later, and oxygenation was normal at discharge on hospital day 4. He also has hypertension. Medications are lisinopril and short-term apixaban for postarthroplasty venous thromboembolism prophylaxis.

On physical examination, vital signs are normal. BMI is 31. Neck circumference is 42 cm (16.5 in). He has a low-lying soft palate. Lung and heart examinations are normal.

Which of the following is the most likely cause of the hypoxemia?

(A) Aspiration pneumonia
(B) Obstructive sleep apnea
(C) Pulmonary edema
(D) Pulmonary embolism

Item 47

A 66-year-old man who is undergoing annual low-dose CT for lung cancer screening is evaluated following the discovery of a solitary 1.5-cm lung nodule in the right upper lobe. There is no lymphadenopathy or effusion seen on the CT scan. He has a chronic cough and a 90-pack-year smoking history. His medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs and the remainder of the physical examination are normal.

Laboratory studies, including liver chemistry tests and measurement of sodium and calcium levels, are normal.

Which of the following is the most appropriate test to perform next?

(A) Endobronchial ultrasonography
(B) High-resolution CT
(C) Integrated PET/CT
(D) Sputum cytology

Item 48

A 29-year-old woman was hospitalized 24 hours ago with hypoxemic respiratory failure due to influenza pneumonia. She was intubated and placed on mechanical ventilation. Treatment includes lactated Ringer solution, intravenous peramivir, propofol, fentanyl, and norepinephrine.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 109/59 mm Hg, pulse rate is 90/min, and respiration rate is 24/min. The arterial $\mathrm{Po_2}$ is 60 mm Hg on $\mathrm{Fio_2}$ of 0.65, and positive end-expiratory pressure is 10 cm H_2O. Tidal volume is 6 mL/kg ideal body weight, and plateau pressure is 27 cm H_2O. The patient is sedated but wakes to touch and is calm. Pulmonary rhonchi are present bilaterally.

Chest radiograph shows bilateral opacities. Echocardiogram reveals normal cardiac function and chamber size.

Which of the following is the most appropriate intervention to improve oxygenation?

(A) Increase level of sedation
(B) Perform recruitment maneuver
(C) Prone positioning
(D) Start diuretics

Item 49

A 55-year-old woman is hospitalized for increased daytime sleepiness that has progressed since discharge from the hospital 2 days ago. She had right knee arthroplasty for osteoarthritis-related severe knee pain. She has a history of obesity, hypertension, and type 2 diabetes mellitus. Medications are lisinopril, metformin, and liraglutide. In addition, she was discharged on oxycodone and enoxaparin.

On physical examination, respiration rate is 12/min; the remainder of the vital signs are normal. BMI is 44. Oxygen saturation is 94% breathing oxygen, 5 L/min by nasal cannula. She is sleepy but easily aroused and cooperative. Lung sounds are distant. A healing surgical wound is present. The remainder of the examination is unremarkable.

Laboratory studies:

Bicarbonate	33 mEq/L (33 mmol/L)
Arterial blood gases:	
pH	7.25
$\mathrm{Pco_2}$	78 mm Hg (10.4 kPa)
$\mathrm{Po_2}$	66 mm Hg (8.8 kPa)

Pulmonary function tests performed 1 month ago demonstrated a restrictive pattern.

Chest radiograph shows small lung fields.

Which of the following is the most appropriate treatment?

(A) Acetazolamide
(B) Bilevel positive airway pressure
(C) Continuous positive airway pressure
(D) Intubation and mechanical ventilation

Item 50

A 58-year-old man hospitalized 5 days ago for a COPD exacerbation is now evaluated for discharge. He required bilevel positive airway pressure for 1 day because of acute hypercapnic and hypoxic respiratory failure. He was treated with prednisone and levofloxacin. This is his second hospitalization for a COPD exacerbation in the past 6 months and the fourth course of prednisone for his COPD in that time. Before hospitalization, his baseline function was limiting dyspnea after walking a few minutes. Medications are inhaled fluticasone furoate-umeclidinium-vilanterol.

On physical examination, oxygen saturation is 96% with the patient breathing ambient air. BMI is 29. He coughs frequently during examination, and faint expiratory wheezing is present in the upper lobes of the lungs. Cardiac examination is normal.

Arterial blood gas studies (at time of discharge):

pH	7.39
$\mathrm{Pco_2}$	43 mm Hg (5.7 kPa)
$\mathrm{Po_2}$	75 mm Hg (10.0 kPa)

Prehospitalization spirometry showed a postbronchodilator reduced $\mathrm{FEV_1/FVC}$ ratio and an $\mathrm{FEV_1}$ of 42% of predicted.

Inhaler technique is reviewed. He is enrolled in a supervised pulmonary rehabilitation program. Immunizations are up to date.

Which of the following is the most appropriate additional treatment?

(A) Nocturnal noninvasive bilevel positive airway pressure ventilation
(B) Roflumilast
(C) Supplemental oxygen
(D) No additional treatment

Item 51

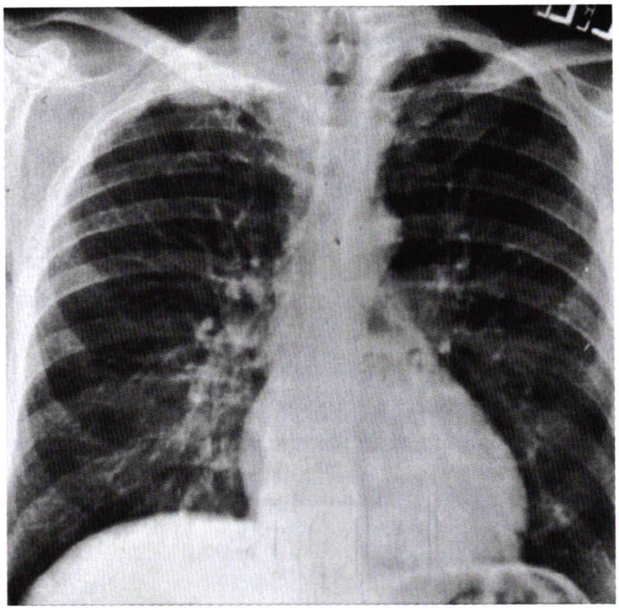
A 55-year-old man is evaluated for a 2-month history of shoulder pain and progressive weakness in his right hand.

The pain radiates to his scapula. He has no shortness of breath or cough. He has a 30-pack-year smoking history and quit smoking 15 years ago. His only medication is ibuprofen for pain.

On physical examination, vital signs are normal. Ptosis and miosis of the right eye are observed. He has mild atrophy of the right hand muscles and decreased grip strength in his right hand. Lungs are clear to auscultation.

Complete blood count and metabolic profile are normal.

Chest radiograph is shown.



Which of the following is the most appropriate next step in management?

(A) Bronchoscopy with biopsy
(B) CT of chest
(C) CT-guided biopsy
(D) Referral for surgical resection

Item 52

A 36-year-old woman is hospitalized with community-acquired pneumonia. She has a history of systemic lupus erythematosus and Raynaud phenomenon, which have been clinically stable with nifedipine and hydroxychloroquine. Levofloxacin was initiated 2 hours ago in the emergency department.

On physical examination, temperature is 37.8 °C (100.0 °F); the remainder of the vital signs are normal. Oxygen saturation by finger pulse oximetry was initially 92% but has decreased to 84% despite the addition of supplemental oxygen at 3 L/min by nasal cannula. Pulmonary examination reveals scattered coarse rhonchi and crackles in the right lower lobe. Cardiac examination is normal. Extremities are cool.

Which of the following is the most appropriate management?

(A) Change to $\mathrm{FIO_2}$ of 0.50 by large-reservoir oxygen mask
(B) Change to earlobe pulse oximetry probe
(C) Obtain arterial blood gases
(D) Obtain CT angiography

Item 53

A 77-year-old man is evaluated in the emergency department following two episodes of melena. He reports no dyspnea or lightheadedness and no hematemesis. Medical history is significant for cirrhosis secondary to hepatitis C virus, which has previously been well compensated. He also has grade 1 esophageal varices but no history of gastrointestinal bleeding. His only medication is propranolol.

On physical examination, the patient is alert and oriented. Temperature is normal, blood pressure is 85/45 mm Hg, pulse rate is 76/min, and respiration rate is 18/min. Oxygen saturation is 97% with the patient breathing ambient air. Icterus is present. Extremities are cool to touch. The abdomen is unremarkable.

Hemoglobin is 6.5 g/dL (65 g/L).

Two peripheral intravenous lines are inserted, and fluid resuscitation with 0.9% saline is initiated.

Which of the following is the most appropriate additional treatment?

(A) Esophageal balloon tamponade
(B) Norepinephrine
(C) Packed red blood cell transfusion
(D) Transjugular intrahepatic portosystemic shunt

Item 54

A 29-year-old man is evaluated in the emergency department after transport by emergency medical services. He was found sitting on his garage floor, lethargic, with an empty container of automotive coolant nearby.

On physical examination, temperature is 37.4 °C (99.3 °F), blood pressure is 108/58 mm Hg, pulse rate is 118/min, respiration rate is 26/min, and oxygen saturation is 99% with the patient breathing ambient air. He arouses briefly to loud voice but is not interactive.

Laboratory studies:

Creatinine	1.3 mg/dL (114.9 µmol/L)
Glucose	Normal
Sodium	138 mEq/L (138 mmol/L)
Potassium	4.8 mEq/L (4.8 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	12 mEq/L (12 mmol/L)
Lactate	Normal
Calculated osmolal gap	Elevated
Arterial blood gas studies:	
pH	7.25
$\mathrm{PCO_2}$	28 mm Hg (3.7 kPa)
$\mathrm{PO_2}$	98 mm Hg (13.0 kPa)

Which of the following is the most appropriate treatment?

(A) Ethanol
(B) Fomepizole
(C) Fomepizole and hemodialysis
(D) Lorazepam

Item 55

A 45-year-old woman is evaluated in the emergency department 2 days after elective laparoscopic cholecystectomy. She is febrile, has emesis, and reports abdominal pain and fullness.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 110/50 mm Hg, pulse rate is 115/min, respiration rate is 28/min, and oxygen saturation is 94% with the patient breathing ambient air. Abdominal examination reveals right-upper-quadrant tenderness and diminished and infrequent bowel sounds. There are decreased breath sounds in the right lung base. The patient is confused. Laparoscopy wounds are intact, with no drainage or erythema.

Which of the following is the best venue of care for this patient?

(A) Emergency department observation unit
(B) General medical ward
(C) ICU
(D) Outpatient

Item 56

A 23-year-old woman is evaluated for chronic cough. She reports several episodes of chronic bronchitis as a child and persistent cough productive of thick purulent sputum since childhood. She also has chronic nasal congestion and chronic diarrhea. Medications are albuterol and glucocorticoid inhalers and benzonatate as needed.

On physical examination, vital signs are normal; oxygen saturation is 96% with the patient breathing ambient air. BMI is 18. Lung examination reveals bilateral diffuse crackles. The remainder of the examination is normal.

Complete blood count and immunoglobulin levels are normal.

Chest CT scan shows bilateral upper-lobe-predominant bronchiectasis with luminal filling.

Spirometry shows an FEV$_1$ of 68% of predicted.

Which of the following is the most likely diagnosis?

(A) Allergic bronchopulmonary aspergillosis
(B) α_1-Antitrypsin deficiency
(C) Cystic fibrosis
(D) IgA deficiency

Item 57

A 45-year-old woman is evaluated in the ICU for septic shock secondary to a necrotic diabetic foot infection. She has not responded to initial resuscitation with 30 mL/kg Ringer lactate infusion and vasopressor therapy. Medications are low-molecular-weight heparin, insulin glargine, norepinephrine, vasopressin, metronidazole, ceftriaxone, and vancomycin.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 78/46 mm Hg, pulse rate is 102/min, and respiration rate is 16/min. Oxygen saturation is 95% with the patient breathing ambient air. A 4-cm diameter, recently debrided ulcer is present over the dorsal metacarpophalangeal joint of the great toe, extending to bone.

Which of the following is the most appropriate additional management?

(A) Cosyntropin stimulation test
(B) Intravenous hydrocortisone
(C) Intravenous immune globulin
(D) Procalcitonin measurement

Item 58

A 25-year-old man is seen in follow-up examination for asthma diagnosed 2 months ago. He reports that his symptoms are now well controlled without use of his rescue inhaler, and results of the Asthma Control Test confirm well-controlled asthma. During the visit, he describes feeling down on many days, with difficulty falling asleep and early morning awakening. Depression screening with the Patient Health Questionnaire-2 is positive. Medications are beclomethasone, montelukast, and albuterol.

On physical examination, vital signs and pulmonary examination are normal.

Which of the following is the most appropriate treatment?

(A) Begin escitalopram
(B) Begin salmeterol
(C) Stop beclomethasone; begin budesonide-formoterol
(D) Stop montelukast

Item 59

A 29-year-old man is evaluated in the hospital for hemorrhagic shock. He has osteogenesis imperfecta and was admitted for a right hip fracture repair 2 days ago. He was placed on low-molecular-weight heparin postoperatively.

Blood pressure is 84/44 mm Hg, pulse rate is 132/min, and respiration rate is 31/min. Oxygen saturation is 91% using a nonrebreather mask. Cardiac examination reveals tachycardia but no murmurs or gallops. He has copious amounts of blood coming from his nose, and there is swelling, bruising, and oozing at the surgical site.

He has an 18-gauge peripheral intravenous catheter in his left forearm.

Which of the following is the most appropriate form of additional intravenous access in this patient?

(A) Peripherally inserted central venous catheter
(B) 18-Gauge peripheral catheter in the right arm
(C) Intraosseous needle in the right humerus
(D) Triple-lumen catheter in the left femoral vein

Item 60

A 55-year-old man is evaluated in the emergency department for abdominal pain and fever of 12 hours' duration.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 90/60 mm Hg, pulse rate is 110/min, and respiration rate is 26/min. Oxygen saturation is 95% with the patient breathing ambient air. The patient is confused. Scleral icterus is noted. There is tenderness to

CONT.

palpation in the right upper quadrant. The remainder of the examination is unremarkable.

Laboratory studies:

Leukocyte count	22,000/µL (22×10^9/L)
Alanine aminotransaminase	448 U/L
Bilirubin	
Total	5.0 mg/dL (85.5 µmol/L)
Direct	4.0 mg/dL (68.4 µmol/L)
Creatinine	2.0 mg/dL (176.8 µmol/L)
Lipase	56 U/L

Ultrasound of the right upper quadrant reveals a normal-appearing liver and gallbladder; the bile duct is dilated.

Which of the following is the most likely diagnosis?

(A) Acute cholangitis
(B) Acute cholecystitis
(C) Pancreatitis
(D) Pyogenic liver abscess

Item 61

A 28-year-old woman is evaluated in the emergency department for severe agitation. The patient is uncooperative. A friend reports that the patient had been snorting cocaine. Paroxetine and tramadol are found in the patient's backpack.

On physical examination, temperature is 39.4 °C (102.9 °F), blood pressure is 164/82 mm Hg, pulse rate is 112/min, respiration rate is 22/min, and oxygen saturation is 98% with the patient breathing ambient air. She is diaphoretic and tremulous. Myoclonus and hyperreflexia are present.

Which of the following is the most appropriate treatment?

(A) Acetaminophen
(B) Fentanyl
(C) Lorazepam
(D) Propranolol

Item 62

A 72-year-old man is evaluated for daytime sleepiness. His wife notes that he snores. He sleeps 8 hours each night. On most days of the week, he feels sleepy and will nap for 45 minutes. Medical history is significant for atrial fibrillation and heart failure. Medications are valsartan-sacubitril, metoprolol, furosemide, spironolactone, empagliflozin, and apixaban.

On physical examination, vital signs are normal. BMI is 27. Low-lying soft palate, irregularly irregular cardiac rhythm, normal central venous pressure, clear lung fields, and chronic venous stasis are present.

Transthoracic echocardiogram obtained 1 year ago showed left ventricular enlargement and left ventricular ejection fraction of 40%.

Which of the following is the most appropriate test?

(A) Actigraphy
(B) Home sleep apnea testing
(C) Overnight oximetry
(D) Polysomnography

Item 63

A 64-year-old woman has been hospitalized for 4 days for a first COPD exacerbation and is now being discharged. Before hospitalization she had mild symptoms such as breathlessness when hurrying on level ground or walking up a slight hill. She stopped smoking 7 years ago. Immunizations are up to date. Medications are a fluticasone furoate-umeclidinium-vilanterol inhaler and an additional day of prednisone.

Today, vital signs are normal. Breath sounds are distant without wheezing. Cardiovascular examination is normal.

A review of the admission chest radiograph shows homogeneous emphysema without other findings. Today, results of laboratory evaluation are normal. Spirometry shows a FEV_1/FVC ratio of 0.6 and an FEV_1 42% of predicted. A 6-minute walk test shows a minimum oxygen saturation of 89% with the patient breathing ambient air.

Which of the following is the most appropriate additional treatment?

(A) α_1-Antitrypsin augmentation therapy
(B) Lung volume reduction surgery
(C) Pulmonary rehabilitation
(D) Supplemental home oxygen

Item 64

A 61-year-old woman is evaluated in the emergency department for a COPD exacerbation characterized by increased dyspnea and increased purulent sputum production. Home medications are mometasone furoate-formoterol, tiotropium bromide, and albuterol inhalers.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 135/82 mm Hg, pulse rate is 112/min, respiration rate is 21/min, and oxygen saturation is 94% breathing oxygen, 5 L/min by nasal cannula. Pulmonary examination reveals diffuse expiratory wheezing but no use of accessory muscles. The remainder of the physical examination is noncontributory.

Arterial blood gas studies:

pH	7.36
P_{CO_2}	43 mm Hg (5.7 kPa)
P_{O_2}	65 mm Hg (8.6 kPa)

Chest radiograph shows hyperinflation and flattened diaphragm but no infiltrate.

Nebulized albuterol and oral azithromycin are initiated.

Which of the following is the most appropriate additional management?

(A) High-flow nasal cannula
(B) Noninvasive bilevel positive airway pressure ventilation
(C) Prednisone
(D) Sputum culture

Item 65

A 48-year-old man is evaluated in the hospital for acute onset of hyperpyrexia and muscle rigidity. He was hospitalized 12 hours ago for upper gastrointestinal bleeding. Within the last hour he underwent upper endoscopy using rapid sequence intubation with succinylcholine and etomidate. Soon after completion of the procedure, he developed fever, tachypnea, and tachycardia.

On physical examination, temperature is 40.6 °C (105.1 °F), blood pressure is 112/68 mm Hg, pulse rate is 130/min, respiration rate is 26/min, and oxygen saturation is 99% breathing oxygen, 2 L/min by nasal cannula. He has generalized muscle rigidity and cannot open his mouth. Neurologic examination is otherwise normal.

Cooling measures are implemented.

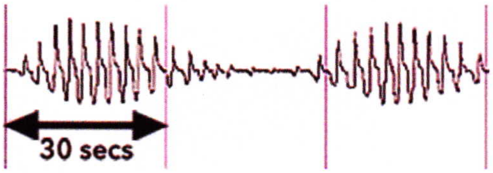
Which of the following is the most appropriate pharmacologic treatment?

(A) Acetaminophen
(B) Cyproheptadine
(C) Dantrolene
(D) Diltiazem

Item 66

A 70-year-old man is evaluated with overnight polysomnography because of fatigue, nocturnal awakenings, and nocturnal dyspnea. He has heart failure with reduced ejection fraction and atrial fibrillation. Medications are metoprolol, valsartan-sacubitril, spironolactone, and rivaroxaban.

Polysomnogram tracing from the respiratory flow channel is shown. An upward deflection indicates inspiration and a downward deflection indicates exhalation.



On physical examination, vital signs are normal. Oxygen saturation is 97% with the patient breathing ambient air. BMI is 23.5. Neck circumference is 39.4 cm (15.5 in). Heart rhythm is irregularly irregular. Lungs are clear.

Which of the following is the most likely diagnosis?

(A) Central sleep apnea
(B) Obstructive sleep apnea
(C) Sleep-related hypoventilation
(D) Treatment-emergent central sleep apnea

Item 67

A 65-year-old woman is evaluated in the emergency department for an acute exacerbation of COPD. Medications are budesonide-formoterol inhaler and albuterol-ipratropium.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 150/95 mm Hg, pulse rate is 100/min, and respiration rate is 30/min. Oxygen saturation is 86% breathing oxygen, 2 L/min by nasal cannula. Bilateral wheezes are present.

Arterial blood gas studies:

pH	7.22
$\mathrm{P}_{\mathrm{CO}_2}$	75 mm Hg (10.0 kPa)
$\mathrm{P}_{\mathrm{O}_2}$	66 mm Hg (8.8 kPa)

Chest radiograph shows no infiltrates.

Which of the following is the most appropriate treatment?

(A) Bilevel positive airway pressure
(B) Continuous positive airway pressure
(C) High-flow nasal cannula
(D) Intubation and mechanical ventilation

Item 68

An 84-year-old man is evaluated in the emergency department for presumed sepsis. He lives in a nursing home, and nurses noted that he was febrile and lethargic. Medical history and medications are not immediately available.

On physical examination, temperature is 39.3 °C (102.7 °F), blood pressure is 88/50 mm Hg, pulse rate is 116/min, and respiration rate is 26/min. Oxygen saturation is 95% breathing oxygen, 3 L/min by nasal cannula. The patient is confused but responds to voice commands. Cardiopulmonary examination reveals tachycardia and normal heart sounds. Rhonchi are auscultated over the left lower lobe.

Crystalloid fluid resuscitation is initiated with a target of 30 mL/kg.

Complete blood count, metabolic panel, lactate, and coagulation studies are pending.

Blood cultures are obtained.

Which of the following is the most appropriate immediate next management step?

(A) Antibiotics
(B) Chest radiography
(C) Intubation
(D) Norepinephrine

Item 69

A 63-year-old woman is evaluated during a routine visit. She has a 37-pack-year history of cigarette smoking and quit smoking at age 55 years. She has COPD but reports no symptoms concerning for lung cancer. Medications are tiotropium inhaler and albuterol inhaler.

Which of the following is the most appropriate lung cancer screening test?

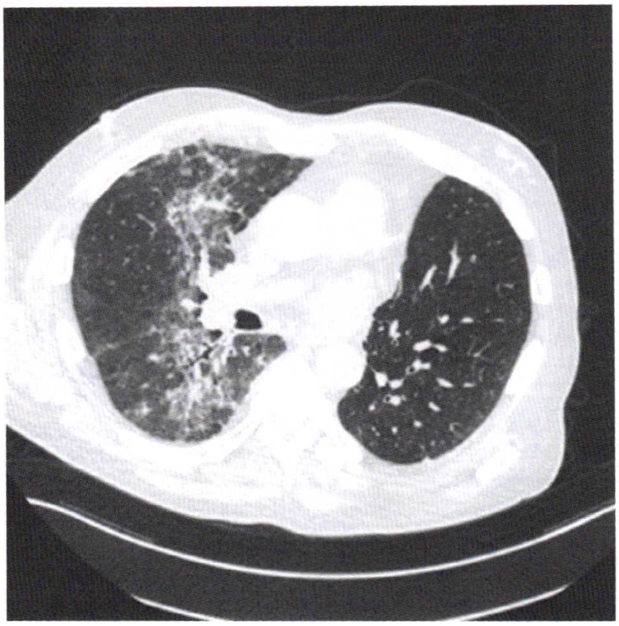
(A) Chest radiography
(B) Fluorodeoxyglucose PET
(C) Low-dose chest CT
(D) Sputum cytology
(E) No screening

Item 70

A 55-year-old man is evaluated in the hospital for fever, dry cough, and shortness of breath of 3 days' duration. He has advanced squamous cell lung cancer, for which he recently started treatment with pembroluzimab. The patient received thoracic radiation to the right hilum 2 months ago.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 110/70 mm Hg, pulse rate is 102/min, and respiration rate is 22/min. Oxygen saturation is 92% with the patient breathing ambient air. BMI is 17. Crackles are present in the right infrascapular region. Cardiovascular examination is normal.

CT scan of the chest is shown.



Bronchoscopy is unremarkable; bronchoalveolar lavage fluid cultures are negative.

Which of the following is the most likely diagnosis?

(A) Hospital-acquired pneumonia
(B) Hypersensitivity pneumonitis
(C) Pulmonary edema
(D) Radiation pneumonitis

Item 71

A 45-year-old woman is evaluated in the ICU for community-acquired pneumonia and septic shock. Appropriate resuscitation efforts are under way.

On physical examination, temperature is 39.2 °C (102.6 °F), blood pressure is 92/50 mm Hg, pulse rate is 120/min, and respiration rate is 25/min. Oxygen saturation is 85% on bilevel positive airway pressure, and $\mathrm{FIO_2}$ is 0.60. Auscultation of the lungs reveals decreased breath sounds over the left lung base.

Chest radiograph reveals scattered infiltrates in the lower lungs with dense consolidation in the left lower lobe and a small left pleural effusion.

Which of the following is the most appropriate diagnostic test for evaluation of the pleural effusion?

(A) Bedside thoracic ultrasonography
(B) Chest CT with contrast
(C) Lateral decubitus film
(D) Thoracic MRI

Item 72

A 54-year-old man is evaluated in the emergency department for shock. He is confused and inattentive. Medical records indicate that he has hypertension, hyperlipidemia, and diabetes. Medications are atorvastatin, metformin, valsartan, and hydrochlorothiazide.

On physical examination, the patient is awake but disoriented. Blood pressure is 82/54 mm Hg, pulse rate is 118/min, and respiration rate is 26/min. Oxygen saturation is 89% with the patient breathing ambient air. Skin is cool and clammy. There is jugular venous distention to the angle of the jaw. Heart sounds are distant but without murmur, rubs, or gallops. Diffuse pulmonary crackles are present.

ECG shows sinus tachycardia (rate 118/min).

Resuscitation efforts are initiated. Portable chest radiography and laboratory studies have been ordered.

Which of the following is the most appropriate additional test?

(A) CT angiography
(B) Pulmonary artery catheterization
(C) Transesophageal echocardiography
(D) Transthoracic echocardiography

Item 73

A 34-year-old woman with fistulizing Crohn disease is evaluated in the ICU 10 days after she was admitted with surgical complications. She has been unable to be weaned from mechanical ventilation. Tube feedings were initiated 48 hours after ICU admission but have not advanced above 50% of her nutritional goal because of recurrent abdominal distention and emesis. She has lost 1.8 kg (4 lb) over the last week. The ileostomy bag contains gas and liquid feces. Medications are low-molecular-weight heparin, metoclopramide, fentanyl, piperacillin-tazobactam, mesalamine, and oral budesonide.

On physical examination, vital signs are normal. BMI is 20. She is intubated, on mechanical ventilation, and a nasogastric feeding tube is in place. She has a healing abdominal surgical wound and an ileostomy. Bowel sounds are present, and the abdomen is distended.

Abdominal radiograph reveals gas throughout the small bowel and no evidence of obstruction.

Which of the following is the most appropriate management?

(A) Add megestrol acetate
(B) Add methylnaltrexone

CONT.

(C) Increase fiber in the enteral diet
(D) Stop enteral nutrition; start parenteral nutrition

Item 74

A 44-year-old woman is evaluated for daytime sleepiness of 1 year's duration. She sleeps 8 to 9 hours nightly. She naps during the day. She has chronic musculoskeletal back pain and depression. Medications are venlafaxine and sustained-release oxycodone.

On physical examination, respiration rate is 12/min; the remainder of the vital signs are normal. She has antalgic gait and limited trunk flexion due to pain. Oropharyngeal airway is patent. Nasal, lung, and heart examinations are normal. There is no peripheral edema.

Polysomnography documents central sleep apnea without obstructive sleep apnea.

Which of the following is the most appropriate treatment?

(A) Adaptive servo-ventilation
(B) Continuous positive airway pressure
(C) Modafinil
(D) Pain rehabilitation program

Item 75

A 64-year-old man is treated in the emergency department for a COPD exacerbation characterized by worsened dyspnea, cough, and increased purulent sputum. Home medications are inhaled fluticasone-vilanterol and tiotropium.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 128/71 mm Hg, pulse rate is 96/min, respiration rate is 18/min, and oxygen saturation is 92% breathing oxygen, 2 L/min by nasal cannula. Lung examination reveals expiratory wheezing and mildly labored respirations. The remainder of the physical examination is normal.

Arterial blood gas studies:

pH	7.39
P_{CO_2}	41 mm Hg (5.4 kPa)
P_{O_2}	61 mm Hg (8.1 kPa)

Chest radiograph shows a flattened diaphragm but no infiltrates or pleural effusions.

Treatment is initiated with prednisone and nebulized albuterol-ipratropium.

Which of the following is the most appropriate additional treatment?

(A) Intravenous theophylline
(B) Intravenous piperacillin-tazobactam
(C) Noninvasive bilevel positive airway pressure ventilation
(D) Oral azithromycin

Item 76

A 55-year-old woman is evaluated for progressive anemia during her 12-day hospital stay. She was hospitalized for pneumonia that progressed to acute respiratory distress syndrome requiring intubation and mechanical ventilation. Since intubation, daily routine laboratory evaluation has detected a slow decline in hemoglobin level from 12.5 g/dL (125 g/L) to the current level of 9.0 g/dL (90 g/L). There is no evidence of bleeding. Medications are propofol infusion, fentanyl infusions, and cefotaxime and levofloxacin.

Laboratory studies document normal platelet and leukocyte counts. The reticulocyte count is elevated, and the peripheral blood smear, other than documenting reticulocytosis, is normal. The direct antiglobulin test is negative, and there is no laboratory evidence of hemolysis.

Which of the following is the most appropriate management?

(A) Discontinue routine blood testing
(B) Erythropoietin administration
(C) Iron studies
(D) Transfusion

Item 77

A 28-year-old woman is evaluated in the emergency department for severe headache and blurred vision of 8 hours' duration. She is 35 weeks pregnant. She has no history of hypertension. Her only medication is a multivitamin.

On physical examination, blood pressure is 200/110 mm Hg, pulse rate is 90/min, and respiration rate is 20/min. Oxygen saturation is 96% with the patient breathing ambient air. No focal neurologic deficits are noted.

Laboratory studies reveal a hemoglobin level of 12 g/dL (120 g/L), a platelet count of 120,000/µL (120×10^9/L), and a urine protein-creatinine ratio of 600 mg/g. Aminotransferase levels are normal.

Blood pressure is reduced to 180/100 mm Hg with intravenous labetalol.

Which of the following is the most appropriate next step in management?

(A) Delivery
(B) Intravenous betamethasone
(C) Intravenous enalapril
(D) Intravenous sodium nitroprusside

Item 78

A 57-year-old woman is evaluated for progressive dyspnea of 1 year's duration. She has otherwise been well and takes no medications.

On physical examination, blood pressure is 121/82 mm Hg. Oxygen saturation is 94% with the patient breathing ambient air. There is a grade 2/6 systolic murmur at the left lower sternal border that increases with inspiration and persistent splitting of S_2. Central venous pressure is elevated. There is a prominent venous *a* wave.

ECG shows right atrial enlargement. Chest radiograph shows prominence of the pulmonary artery. Echocardiogram reveals a right ventricular systolic pressure of 64 mm Hg and an estimated right atrial pressure of 15 mm Hg.

Left ventricular function is normal. Pulmonary function tests show decreased DLCO but are otherwise normal. Ventilation/perfusion scan is low probability for pulmonary embolism.

Which of the following is the most appropriate management?

(A) Coronary angiography
(B) Right heart catheterization
(C) Start nifedipine
(D) Start sildenafil

Item 79

A 22-year-old man is evaluated in the emergency department (ED) after being pulled from a partially frozen lake. Immersion time is estimated to be 2 hours. He was found by emergency medical services and was unresponsive and pulseless. He was intubated, and advanced life support was initiated. On arrival at the ED, pulse had returned and cardiopulmonary resuscitation was stopped. Mechanical ventilation was initiated, and intravenous fluids were administered. Wet clothes were removed.

On physical examination, blood pressure is 92/60 mm Hg. Temperature by an esophageal probe is 27.6 °C (81.7 °F). There are no signs of trauma.

Laboratory studies:

Glucose	88 mg/dL (4.9 mmol/L)
Potassium	5.4 mEq/L (5.4 mmol/L)
Arterial blood gas studies:	
pH	7.28
Pco_2	36 mm Hg (4.8 kPa)
Po_2	110 mm Hg (14.6 kPa)

Which of the following is the most appropriate warming technique?

(A) Active internal rewarming
(B) Cardiopulmonary bypass warming
(C) Hemodialysis
(D) Passive rewarming

Item 80

A 54-year-old man is evaluated during a follow-up visit for asthma. He has a 5-year history of persistent asthma. He has had one exacerbation within the last year, which was treated with glucocorticoids. He reports no wheezing but notes an intermittent nonproductive cough. His Asthma Control Test score is 24, indicating well-controlled asthma. He reports adherence to his maintenance inhaler and demonstrates good inhaler technique. He describes symptoms of epigastric burning following meals. He has no other gastrointestinal symptoms. He does not smoke, and he exercises daily without limitation. Medications are fluticasone-salmeterol 100/50 µg and an albuterol inhaler.

On physical examination, vital signs are normal, and no wheezing is noted. Spirometry is normal. Fractional exhaled nitric oxide level is normal.

Which of the following is the most appropriate management?

(A) Begin omeprazole
(B) Discontinue fluticasone-salmeterol; begin fluticasone 250 µg
(C) Increase fluticasone-salmeterol strength to 500/50 µg
(D) Perform upper endoscopy

Item 81

A 67-year-old woman is evaluated for a 6-month history of dull right chest pain, persistent cough, and dyspnea on exertion. During this time she lost 9.1 kg (20 lb) and had night sweats. She is a retired ship refitter. She has a 25-pack-year smoking history and quit smoking 20 years ago.

On physical examination, vital signs are normal. There are diminished breath sounds and dullness to percussion over the right lower hemithorax. Cardiac examination is normal.

Chest radiograph demonstrates a large pleural effusion on the right side as well as pleural plaques. Chest CT scan shows basilar fibrosis and moderate to large right-sided pleural effusion with associated pleural thickening and nodularity.

Thoracentesis yields 1200 mL of serosanguinous fluid; chemical analysis is compatible with an exudative effusion. Interferon-γ release assay is negative. Cytology findings are negative for malignancy.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Closed pleural biopsy
(B) Fluorodeoxyglucose PET
(C) Repeat thoracentesis
(D) Thoracoscopic pleural biopsy

Item 82

A 67-year-old man is evaluated before airline travel. He is planning a trip to Hawaii next month. He has COPD and becomes dyspneic when walking short distances on level ground. Results of his last pulmonary function test indicated an FEV$_1$ of 40% of predicted. He has not yet required oxygen supplementation. Medications are tiotropium, salmeterol, and fluticasone and albuterol inhalers.

On physical examination, respiration rate is 16/min. Auscultation of the lungs reveals a prolonged expiratory phase with no wheezes.

Which of the following is the most appropriate next step?

(A) High-altitude simulation test
(B) Recommend against air travel
(C) Resting pulse oximetry
(D) No further testing needed

Item 83

A 32-year-old woman is evaluated in the hospital for a 3-week history of progressive shortness of breath, arthralgia,

CONT.

and fatigue. Her only medication is pantoprazole for gastroesophageal reflux disease. Medical history is significant for Raynaud phenomenon treated with cold avoidance. She works in an accounting firm and has no unusual environmental exposures.

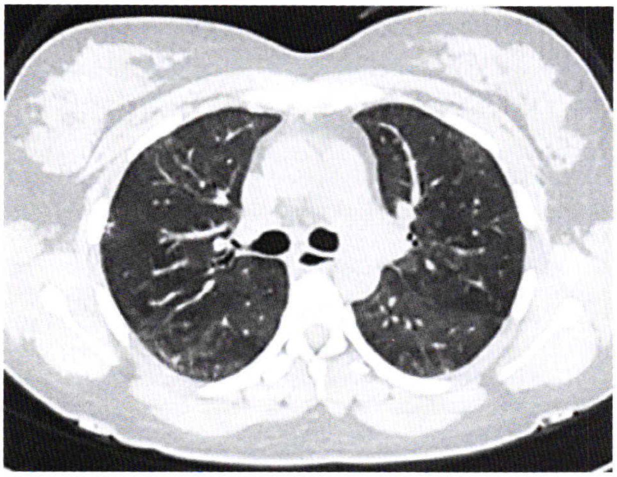
On physical examination, blood pressure is 140/90 mm Hg, pulse rate is 98/min, and respiration rate is 24/min. Oxygen saturation is 90% breathing oxygen, 2 L/min by nasal cannula. Auscultation reveals crackles at both lung bases. She has puffy-appearing fingers. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	11 g/dL (110 g/L)
C-reactive protein	4 mg/dL (40 mg/L)
Antinuclear antibody	Positive
Antitopoisomerase I (anti-Scl-70) antibody	Positive

Chest radiograph shows bilaterally increased markings with a basilar predominance without lymphadenopathy.

Chest CT is shown.



Which of the following is the most likely diagnosis?

(A) Connective tissue disease–associated interstitial lung disease
(B) Hypersensitivity pneumonitis
(C) Idiopathic pulmonary fibrosis
(D) Sarcoidosis

Item 84

A 66-year-old woman is evaluated for stress ulcer prophylaxis. She has been in the ICU on mechanical ventilation for 72 hours for respiratory failure due to community-acquired pneumonia. She has required vasopressors and glucocorticoids to maintain her blood pressure. She has acute kidney injury. Medications are ceftaroline, levofloxacin, norepinephrine, dexamethasone, and low-molecular-weight heparin. She is receiving enteral nutrition through a feeding tube.

The decision is made to initiate stress ulcer prophylaxis with an oral proton pump inhibitor.

A reduction in which of the following outcomes is most likely with this preventive strategy?

(A) Gastrointestinal bleeding
(B) Hospital stay
(C) ICU stay
(D) Mortality

Item 85

A 34-year-old man is evaluated at a routine follow-up examination. He has a history of spirometry-confirmed asthma. He reports feeling well and denies sinus symptoms, gastroesophageal reflux disease, and tobacco use. He demonstrates excellent inhaler technique. Medications are inhaled budesonide and albuterol.

On physical examination, vital signs are normal, and the remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in evaluation?

(A) Administer the Asthma Control Test
(B) Measure fractional exhaled nitric oxide
(C) Obtain chest radiograph
(D) Perform 6-minute walk test

Item 86

A 66-year-old woman is evaluated in the ICU for management of acute hypoxic respiratory failure due to viral pneumonia. She has no other medical problems and takes no medications.

On physical examination, the patient is calm, alert, and interactive. Temperature is 37.6 °C (99.7 °F), blood pressure is 140/90 mm Hg, pulse rate is 100/min, and respiration rate is 32/min. Oxygen saturation is 89% breathing oxygen, 3 L/min by nasal cannula. Lung examination reveals bilateral rhonchi and tachypnea. Cardiac examination is normal.

On arterial blood gas analysis with the patient breathing ambient air, pH is 7.40, P_{CO_2} is 37 mm Hg (4.9 kPa), and P_{O_2} is 58 mm Hg (7.7 kPa).

Chest radiograph shows bilateral opacities.

Therapy is initiated.

Which of the following is the most appropriate additional management of the patient's hypoxemia?

(A) Intubation and mechanical ventilation
(B) No change in current management
(C) Noninvasive positive pressure ventilation
(D) Oxygen by high-flow humidified nasal cannula

Item 87

A 62-year-old man is evaluated during a follow-up visit for COPD. He continues to smoke one pack daily and has a 40-pack-year history. He can walk rapidly on a level surface but has breathlessness walking up a slight hill. He has not been hospitalized or seen urgently for an exacerbation. Medications are salmeterol and tiotropium.

On physical examination, vital signs are normal. Oxygen saturation is 92% with the patient breathing ambient air. Faint expiratory wheezing is present.

Spirometry shows an FEV_1/FVC ratio of 0.58, and FEV_1 is 62% of predicted.

Which of the following is the most appropriate additional therapy?

(A) Chronic azithromycin therapy
(B) Prednisone
(C) Pulmonary rehabilitation
(D) Smoking cessation

Item 88

A 54-year-old man is evaluated for a 2-year history of chronic productive cough. He has intermittent wheezing, shortness of breath with exertion, and nasal congestion.

On physical examination, vital signs are normal. Bibasilar crackles are present. Cardiac examination is normal.

CT scan of the chest shows cylindrical bronchiectasis of bilateral lower lobes.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bronchoscopy with bronchoalveolar lavage
(B) Immunoglobulin measurement
(C) Measurement of IgG response to pneumococcal immunization
(D) Nasal ciliary biopsy

Item 89

A 22-year-old man is evaluated for a 6-week history of shortness of breath and cough. He is otherwise healthy and takes no medications. He works from home as a software developer. Two months ago, he acquired a pet parakeet.

On physical examination, other than a respiratory rate of 25/min, vital signs are normal. Oxygen saturation is 93% with the patient breathing ambient air. Auscultation demonstrates inspiratory crackles over both lung fields. The remainder of the physical examination is normal.

Chest CT shows micronodular opacities in the mid- to upper-lung zones.

Which of the following is the most appropriate management?

(A) Lung transplant
(B) Nintedanib
(C) Parakeet removal
(D) Surgical lung biopsy

Item 90

A 34-year-old man is evaluated in the emergency department after being found unresponsive in a homeless shelter with two empty bottles of hand sanitizer. The pertinent listed ingredients of the hand sanitizer are ethanol and isopropyl alcohol. The patient has a history of chronic alcoholism.

On physical examination, temperature is normal, blood pressure is 112/68 mm Hg, pulse rate is 94/min, respiration rate is 14/min, and oxygen saturation is 96% breathing oxygen, 2 L/min by nasal cannula. He arouses to painful stimuli. His speech is slurred, and he shows psychomotor slowing. Neurologic examination is otherwise normal.

The calculated anion gap is normal; the osmolal gap is elevated.

Which of the following is the most appropriate management?

(A) Ethanol
(B) Flumazenil
(C) Fomepizole
(D) Hemodialysis
(E) Supportive care

Item 91

A 63-year-old woman is evaluated for increasing shortness of breath for the past 2 months. She has ischemic cardiomyopathy and a history of breast cancer treated with surgery and irradiation 9 years ago. When she was between 20 and 30 years of age, she worked installing brakes on automobiles. She is on guideline-directed medical therapy for heart failure.

On physical examination, vital signs normal. Cardiac examination reveals an S_3, mitral regurgitation, hepatomegaly, possible ascites, and peripheral edema. There is dullness to percussion and absent breath sounds at the left base.

Chest radiograph shows a moderate left-sided pleural effusion but is otherwise normal.

A thoracentesis removes 600 mL of bloody fluid. The pleural fluid lactate dehydrogenase (LDH) level is 208 U/L, and the total protein level is 4.4 g/L. Simultaneous serum LDH level is 279 U/L, and total protein level is 7.6 U/L. Pleural fluid cytology is pending.

Which of the following is the most likely diagnosis?

(A) Benign asbestos pleural effusion
(B) Heart failure
(C) Hepatic hydrothorax
(D) Malignant pleural effusion

Item 92

A 54-year-old man is evaluated for nutritional supplementation. He was admitted to the ICU 3 days ago for sepsis related to an empyema associated with community-acquired pneumonia. He was unable to maintain his nutritional needs before admission, and this has continued during hospitalization. He has lost an unknown quantity of weight. A decision is made to begin enteral feedings. His nutritional requirements are calculated to be 1460 calories daily.

H

CONT.

Which of the following is the most appropriate enteral feeding strategy for this patient?

(A) 1460 calories daily starting on day 1
(B) 2000 calories daily starting on day 1
(C) Incremental increase to 1460 calories daily over 3 to 7 days
(D) Incremental increase to 2000 calories daily over 3 to 7 days

Item 93

A 24-year-old woman is evaluated for intermittent cough, wheezing, and chest tightness of 1 month's duration. She reports worsening symptoms with exercise and with cat exposure.

On physical examination, vital signs are normal. She has end-expiratory wheezing. Cardiac examination is normal.

On spirometry, FEV_1 is 75% of predicted and improves significantly following inhaled albuterol.

Which of the following tests will help predict this patient's responsiveness to inhaled glucocorticoids?

(A) Bronchial challenge testing
(B) Diffusing capacity for carbon monoxide
(C) Fractional exhaled nitric oxide
(D) Pulse oximetry

H

Item 94

A 44-year-old woman is evaluated 1 day after right mastectomy for breast cancer. Desaturations throughout the night necessitated oxygen initiation. Medications are an oral opioid and subcutaneous enoxaparin.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 140/60 mm Hg, pulse rate is 90/min, and respiration rate is 28/min. Oxygen saturation is 93% breathing oxygen, 6 L/min by nasal cannula. The patient has shallow breathing with splinting. Lung examination reveals diminished breath sounds at the right lung base, dullness on percussion, egophony in the right lower lobe, and rhonchi. The remainder of the examination is normal.

Chest radiograph shows plate-like opacities in the lung bases consistent with atelectasis.

Which of the following is the most appropriate management?

(A) Bronchoscopy
(B) Inhaled albuterol
(C) Inhaled *N*-acetylcysteine
(D) Pain management

H

Item 95

A 33-year-old woman is evaluated in the emergency department for respiratory failure. She has a 1-week history of ascending lower-extremity weakness and paresthesia. She has developed progressive dyspnea over the past 48 hours.

On physical examination, the patient is alert and cooperative. Blood pressure is 150/90 mm Hg, pulse rate is 100/min, and respiration rate is 26/min. Oxygen saturation is 93% with the patient breathing ambient air. Cardiopulmonary examination is normal. Neurologic examination shows moderate weakness of her feet, legs, hands, and arms. Diffuse areflexia is present but sensation is normal.

Arterial blood gas studies:

pH	7.34
P_{CO_2}	49 mm Hg (6.5 kPa)
P_{O_2}	80 mm Hg (10.6 kPa)
Alveolar-arterial oxygen gradient	Normal

Chest radiograph is normal.

There is a 22% decrement in forced vital capacity while supine compared with the upright position. Maximal inspiratory pressure and maximal expiratory pressure are both less than 50% of predicted.

Which of the following is the most likely cause of this patient's respiratory failure?

(A) Decreased ventilatory drive
(B) Hypoxemic respiratory failure
(C) Neuromuscular weakness
(D) Pulmonary embolism

Item 96

H

An 84-year-old man is evaluated 3 days after he was admitted to the ICU with a right lower lobe infiltrate and presumed sepsis. On the day of admission, the patient vomited, aspirated, and developed respiratory distress. In the emergency department, temperature was 38.3 °C (100.9 °F); tachypnea, tachycardia, hypoxemia, and hypotension were also present. Chest radiograph on admission showed an infiltrate in the right lower lobe. Intravenous fluids, supplemental oxygen by nasal cannula, and broad-spectrum antibiotics were given. Over the next 24 hours, the patient improved rapidly.

On today's physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 138/80 mm Hg, pulse rate is 66/min, and respiration rate is 16/min. Oxygen saturation is 95% with the patient breathing ambient air.

The patient's leukocyte count is 6,000/µL (6×10^9/L) with a normal differential.

Sputum and blood cultures are negative.

Which of the following is the most appropriate antibiotic management?

(A) Continue antibiotics for 4 additional days
(B) Continue antibiotics for 7 additional days
(C) Continue antibiotics for 10 additional days
(D) Discontinue antibiotics

Item 97

A 62-year-old man is evaluated for chronic cough productive of thin clear sputum and dyspnea on exertion that has worsened over the last 2 years. He has a 54-pack-year smoking history. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. The patient coughs during the examination, and mild expiratory wheezing is heard over the posterior lung fields. Cardiac examination is normal.

Chest radiograph shows hyperinflated lungs with a flattened diaphragm without infiltrates.

Spirometry shows an FEV_1/FVC ratio of 0.65 and an FEV_1 of 52% of predicted without a significant bronchodilator response.

Which of the following is the most likely diagnosis?

(A) Asthma
(B) Bronchiectasis
(C) COPD
(D) Desquamative interstitial pneumonia

Item 98

A 72-year-old man is evaluated for exertional dyspnea of 1 year's duration and recent onset of orthopnea. He has diabetes mellitus, hypertension, and coronary artery disease. Medications are atorvastatin, aspirin, lisinopril, metoprolol, and metformin.

On physical examination, blood pressure is 150/82 mm Hg; the remaining vital signs are normal. Jugular venous pressure is elevated. An S_3 is present. Pulmonary examination reveals occasional crackles. There is 2+ pitting edema to the knees.

A chest radiograph shows an enlarged cardiac silhouette and pulmonary vascular congestion.

An echocardiogram reveals a left ventricular ejection fraction of 20% and a right ventricular systolic pressure of 50 mm Hg.

Which of the following is the most likely cause of the patient's pulmonary hypertension?

(A) Chronic thromboembolic pulmonary hypertension
(B) Idiopathic pulmonary arterial hypertension
(C) Interstitial lung disease
(D) Left ventricular failure

Item 99

A 55-year-old man presents for follow-up evaluation 1 week after an emergency department visit for abdominal pain. A CT scan of the abdomen showed a 7-mm lung nodule in the right lower lobe. No previous images of the chest are available. The patient's abdominal pain has since resolved. He is a lifelong nonsmoker and has no occupational or recreational exposure to carcinogens. Family history is unremarkable.

On physical examination, vital signs and other examination findings are normal.

A dedicated thin-section chest CT scan demonstrates a 7-mm noncalcified nodule with smooth contours. The rest of the chest CT scan is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Bronchoscopy with biopsy
(B) Fluorodeoxyglucose PET/CT
(C) Repeat chest CT in 6 months
(D) Surgical resection

Item 100

A 69-year-old man is evaluated in the hospital for shortness of breath 24 hours after admission for left inferior pubic ramus fracture. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, the patient is confused. Temperature is 38.2 °C (100.8 °F), blood pressure is 104/68 mm Hg, pulse rate is 110/min, and respiration rate is 26/min. Oxygen saturation is 90% breathing oxygen, 3 L/min by nasal cannula. There are crackles at both lung bases. Petechiae are present over the neck and upper trunk.

Chest radiograph reveals patchy infiltrates at the bases.

Which of the following is the most likely diagnosis?

(A) Air embolism
(B) Fat embolism syndrome
(C) Hospital-acquired pneumonia
(D) Pulmonary embolism

Item 101

A 42-year-old man with 6 months of progressive dyspnea is diagnosed with chronic thromboembolic pulmonary hypertension following right heart catheterization and pulmonary artery angiography. Medical history is otherwise unremarkable, and he takes no medications.

Apixaban is initiated.

Which of the following is the most appropriate management?

(A) Add riociguat
(B) Balloon pulmonary angioplasty evaluation
(C) Surgical thromboendarterectomy evaluation
(D) No additional treatment

Item 102

A 32-year-old woman is evaluated for an asthma exacerbation. She previously had well-controlled asthma. She has increased the use of her maintenance inhaler and is using her rescue medication four times daily, but her symptoms persist. She reports no fever, chills, chest pain, or purulent sputum. She has no history of intubation, emergency department visits, or hospitalizations for asthma and has adhered to her medication regimen. She is a nonsmoker. Medications are inhaled budesonide and albuterol.

On physical examination, respiration rate is 25/min; the remainder of vital signs are normal. Oxygen saturation is 96% with the patient breathing ambient air. The patient is not using accessory muscles of respiration and is able to speak in full sentences. There is scattered expiratory wheezing.

Which of the following is the most appropriate treatment?

(A) Doxycycline, 5-day course
(B) Intravenous methylprednisone, followed by a 5-day prednisone course

(C) Prednisone, 5-day course

(D) Prednisone, 14-day course

(E) Switch to budesonide-formoterol

H Item 103

A 72-year-old woman is evaluated for exacerbation of bronchiectasis symptoms over the past 3 days. Chronic productive cough has worsened in frequency and severity, and her sputum has increased in amount, become thicker, and changed in color from white to dark yellow. She has been using albuterol and hypertonic saline nebulization with a positive expiratory pressure device three times daily since her symptoms increased.

On physical examination, vital signs are normal. Lung examination reveals bibasilar crackles. There is no accessory muscle use.

Prior sputum cultures have grown *Pseudomonas aeruginosa* and *Haemophilus parainfluenzae*.

Chest radiograph reveals chronic interstitial markings but no acute change.

Which of the following is the most appropriate treatment?

(A) Azithromycin

(B) Ciprofloxacin

(C) Inhaled dornase alfa

(D) Prednisone

Answers and Critiques

H

Item 1 Answer: A

Educational Objective: Prevent delirium with early mobilization.

The most appropriate management is early mobilization (**Option A**). Delirium is characterized by an acute change in cognitive functioning occurring over hours to days, with fluctuations during the course of the day. Features of delirium include inattention, disorganized thinking, executive dysfunction, altered level of consciousness (lethargy or hypervigilance), perceptual disturbances (hallucinations or delusions), altered psychomotor activity (hyperactivity, hypoactivity, or alternating periods of hyperactivity and hypoactivity), sleep-wake disturbances, and labile mood. It is extremely common in patients in the ICU and is associated with increased length of ICU stay, morbidity, mortality, and cognitive impairment. Risk factors for delirium include preexisting dementia, hypertension, alcoholism, and high severity of illness on ICU admission. Patients should be monitored regularly and assessed using scales such as the Confusion Assessment Method-ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC). Measures to decrease the risk of delirium include early mobilization, preservation of nocturnal sleep, adequate pain management, orientation of the patient, provision of visual and hearing aids, and minimization of nonessential medications. Early mobilization, consisting of interruption of sedation followed by physical and occupational therapy in the earliest days of critical illness, can be effective for treating and preventing delirium.

Several pharmacologic strategies, including haloperidol (**Option B**), have been attempted to prevent delirium in critically ill patients. None have proved effective. Several of these medications (aripiprazole and haloperidol) have been added to the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Thus, minimizing factors that are known to increase the risk for delirium remains the main focus of care of critically ill patients.

In general, benzodiazepines such as lorazepam (**Option C**) should not be used for treating delirium in the ICU unless needed in patients with alcohol withdrawal or seizures. In the absence of these indications, benzodiazepines such as lorazepam may increase the risk of delirium.

Melatonin (**Option D**) is a popular medication prescribed with an aim to maintain the sleep cycle, which in turn may prevent delirium. The data on its effect in promoting sleep or preventing delirium are inconsistent, and thus it is not recommended as a routine delirium prevention strategy.

KEY POINTS

- Measures to decrease the risk of delirium include early mobilization, preservation of nocturnal sleep, adequate pain management, orientation of the patient, provision of visual and hearing aids, and minimization of nonessential medications.
- Except in treating alcohol withdrawal, pharmacologic strategies are ineffective in the prevention and treatment of delirium.

Bibliography

Blair GJ, Mehmood T, Rudnick M, et al. Nonpharmacologic and medication minimization strategies for the prevention and treatment of ICU delirium: A narrative review. J Intensive Care Med. 2019;34:183-190. [PMID: 29699467] doi:10.1177/0885066618771528

Item 2 Answer: C

Educational Objective: Treat obstructive sleep apnea with an oral appliance.

The most appropriate treatment alternative to continuous positive airway pressure (CPAP) in this patient is an oral appliance (**Option C**). This patient has symptomatic obstructive sleep apnea (OSA) of moderate severity. OSA severity improves with weight loss, so all patients with overweight or obesity should be counseled accordingly. In minimally symptomatic patients with mild OSA, weight loss might be preferred therapy. Additional measures that may help mild OSA include reducing alcohol intake before bedtime, avoiding sedating medications (benzodiazepines, opioids), and avoiding a supine posture if OSA is position dependent. Although CPAP improves symptoms and is generally the preferred treatment for OSA, patient preference or intolerance to CPAP should prompt consideration of other treatments. Oral appliances increase upper airway caliber primarily by exerting traction to advance the mandible. Randomized controlled trials of these appliances have demonstrated good control of mild to moderate OSA and improvement in symptoms such as daytime sleepiness.

A hypoglossal nerve stimulator (**Option A**) is implanted in the chest wall and synchronizes with the respiratory cycle to contract the tongue muscles during inspiration. A multicenter clinical trial demonstrated its efficacy in OSA, including severe disease; however, there are criteria for patient selection, and the procedure is not recommended for patients with a BMI greater than 32. This patient's BMI of 34 would exclude him from candidacy. Although hypoglossal nerve stimulation is efficacious in select patients, it is invasive and more costly than CPAP and oral appliances and is not the best initial option for this patient.

Case series have demonstrated significant improvements in apnea-hypopnea index following maxillomandibular advancement surgery (**Option B**), but in most patients this procedure would not be considered a primary treatment. Evidence supporting upper airway surgical procedures to treat OSA is limited. Patient selection is not standardized, and neurocognitive outcomes are unknown or inconsistent.

Literature on uvulopalatopharyngoplasty (**Option D**), a soft palatal procedure, shows only limited improvements in apnea-hypopnea index. Trial data are beginning to emerge, but at this time, the procedure should generally not be recommended for primary treatment of OSA.

KEY POINTS

- Obstructive sleep apnea (OSA) severity improves with weight loss; in minimally symptomatic patients with mild OSA, weight loss might be the preferred therapy.
- Although continuous positive airway pressure (CPAP) is generally the preferred treatment for obstructive sleep apnea, patient preference or intolerance to CPAP should prompt consideration of other treatments such as an oral appliance.

Bibliography

Patel SR. Obstructive sleep apnea. Ann Intern Med. 2019;171:ITC81-ITC96. [PMID: 31791057] doi:10.7326/AITC201912030

Item 3 Answer: A

Educational Objective: Manage primary spontaneous pneumothorax in a patient with a high-risk occupation.

The most appropriate additional management is catheter thoracostomy followed by pleurodesis (**Option A**). The patient has a spontaneous pneumothorax. Because he has no known underlying lung disease, this would be classified as a primary spontaneous pneumothorax (PSP). A secondary spontaneous pneumothorax (SSP) occurs in someone with known underlying lung disease, such as COPD. The risk of recurrence after an initial occurrence of a PSP is 17% to 54% in the first year. Cigarette smoking is the most important risk factor for PSP. The relative risk of a first event of PSP is 22-fold higher in men and 9 times higher in women who smoke tobacco than in those who do not smoke. The patient should be counseled to stop smoking and offered pharmacologic assistance. Other risk factors include tall height and a low body mass index. Treatment for a first episode of PSP is observation, oxygen and observation, needle aspiration, or placement of a small-bore thoracostomy, depending on symptomatology. Definitive treatment with pleurodesis to prevent recurrence is usually not provided until a second ipsilateral event has occurred, unless the patient's occupation is considered high risk. This patient is a professional scuba diver and is at high risk of death if he has a recurrence while diving. Flying at high altitude is also considered a high-risk occupation. Given the patient's occupation, a more definitive management plan should be pursued following insertion of tube thoracostomy with either mechanical or talc pleurodesis.

Recurrence prevention is recommended after the second episode of pneumothorax on the ipsilateral side in PSP and after the first occurrence in SSP due to the high recurrence rate (>50%). Depending on size and symptoms, needle aspiration (**Option B**), observation (**Option C**), and oxygen and observation (**Option D**) would all be appropriate options in a patient with a first episode of PSP who did not have a high-risk occupation. However, because this patient has a high-risk occupation, definitive therapy should be provided following a first episode of PSP.

KEY POINTS

- Recurrence prevention is recommended after the second episode of pneumothorax on the ipsilateral side in primary spontaneous pneumothorax and after the first occurrence in secondary spontaneous pneumothorax.
- Recurrence prevention is indicated following a first episode of pneumothorax in spontaneous primary pneumothorax in a patient with a high-risk occupation.

Bibliography

Tschopp JM, Bintcliffe O, Astoul P, et al. ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. Eur Respir J. 2015; 46:321-35. [PMID: 26113675] doi:10.1183/09031936.00219214

Item 4 Answer: C

Educational Objective: Treat nonexertional heat stroke.

The most appropriate treatment is evaporative cooling with water mist, fans, and ice packs (**Option C**). Heat stroke is a failure of the body's thermal regulatory system caused by dysfunction, as in elderly patients taking anticholinergic medications; volume depletion (diuretics, insensible water loss); or overwhelming of the system, as in athletes or military recruits who train strenuously in hot, humid weather. They may also experience hypotension, nausea, and muscle weakness. This patient has nonexertional heat stroke. It is generally defined by a core body temperature above 40 °C (104.0 °F) along with encephalopathy. Additional complications of heat stroke can include kidney and liver injury, disseminated intravascular coagulation, and rhabdomyolysis. The elderly are particularly vulnerable, with added risk from comorbidities and medications. If untreated, mortality in heat stroke can reach 60%. Treatment of nonexertional heat stroke includes evaporative cooling (with water mist and fans) with or without ice packs to lower the core temperature to a safe temperature, usually 38.5 °C (101.3 °F). Evaporative cooling is effective, noninvasive, and easily performed, and does not interfere with other aspects of patient care. It is associated with decreased morbidity and mortality when used to treat elderly patients with classic heat stroke.

Centrally acting antipyretics such as acetaminophen (**Option A**) are not effective for heat stroke because the underlying mechanism does not involve a change in the hypothalamic set point. Furthermore, acetaminophen may exacerbate complications such as hepatic injury and should be avoided.

Malignant hyperthermia is a rare cause of severe hyperthermia in response to inhaled anesthetic agents (e.g., halothane and isoflurane) or depolarizing paralytic agents (e.g., succinylcholine) (**Option B**). When a patient with inherited susceptibility is exposed to one of these agents, he or she may develop muscle rigidity, rhabdomyolysis, cardiac arrhythmias, and core body temperature elevation to 45.0 °C (113.0 °F) or more. Mortality can reach 10%. Treatment consists of discontinuing the triggering agent, active cooling, and administration of the muscle relaxant dantrolene every 5 to 10 minutes until muscle rigidity and hyperthermia resolve. Dantrolene is ineffective in patients with severe temperature elevation not caused by malignant hyperthermia.

Immersion in ice water (**Option D**) may be necessary in young persons with exertional heat stroke when they remain severely symptomatic despite evaporative cooling, but it is not first-line therapy because it may be complicated by hypothermia. In older persons with nonexertional hyperthermia, ice water immersion is associated with increased mortality and should not be used.

KEY POINTS

- Treatment of nonexertional heat stroke includes evaporative cooling (with water mist and fans) with or without ice packs to lower the core temperature to a safe temperature, usually 38.5 °C (101.3 °F).
- In older persons with nonexertional hyperthermia, ice water immersion is associated with increased mortality and should not be used.

Bibliography

Epstein Y, Yanovich R. Heatstroke. N Engl J Med. 2019;380:2449-2459. [PMID: 31216400] doi:10.1056/NEJMra1810762

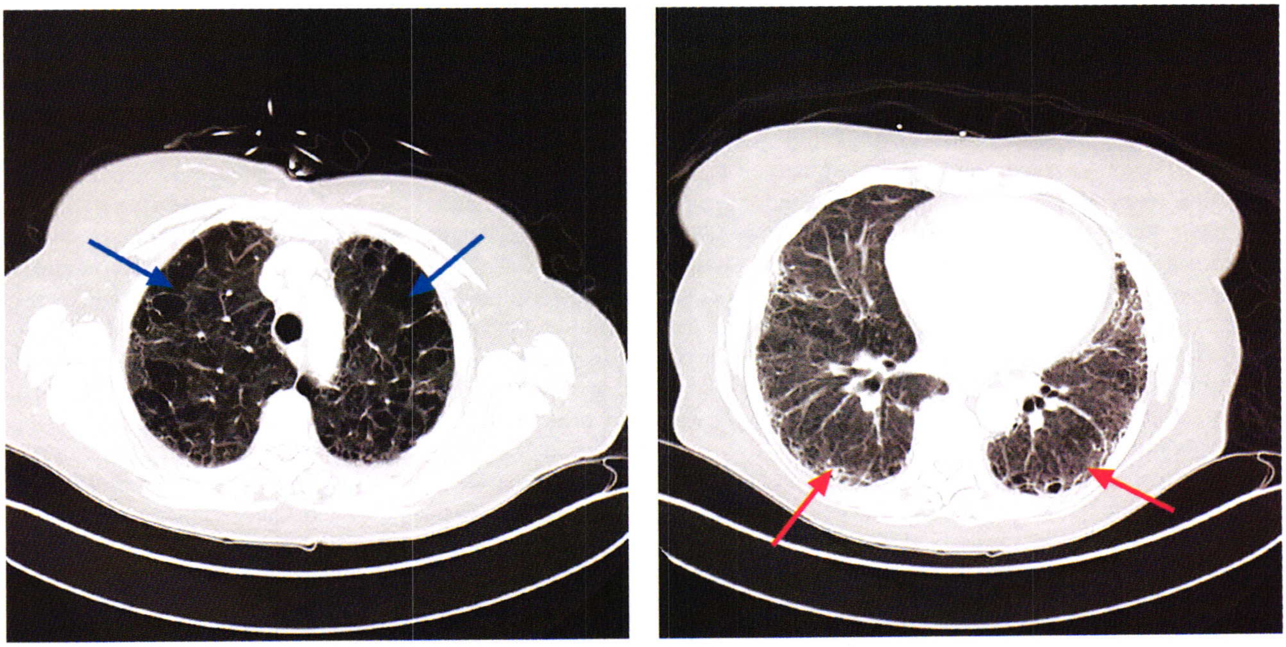
Item 5 Answer: B

Educational Objective: Diagnose combined pulmonary fibrosis and emphysema.

The most likely diagnosis is combined pulmonary fibrosis and emphysema (CPFE) (**Option B**), a unique pathophysiologic entity distinct from either idiopathic pulmonary fibrosis (IPF) or emphysema. In patients with CPFE, the competing effects of emphysema and fibrosis result in higher lung volumes than are found in patients with pulmonary fibrosis alone. Similarly, the FEV_1/FVC ratio in patients with CPFE may be preserved. However, there appears to be an additive deleterious effect on gas exchange properties of the lungs, resulting in a severe reduction in the DLCO. High-resolution CT (HRCT) is the preferred diagnostic modality to demonstrate upper-lobe emphysema (blue arrows, left panel below) and lower-lobe fibrosis (red arrows, right panel below), as shown below. The likelihood of the development of pulmonary hypertension in CPFE is much higher than in either COPD or IPF. The presence of pulmonary hypertension in CPFE portends a poor prognosis.

Acute interstitial pneumonia (AIP) (**Option A**) is a rapidly progressing illness resulting in acute respiratory failure over days to weeks. This process is clinically, radiographically, and pathologically indistinguishable from acute respiratory distress syndrome. The patient's radiograph showing upper-lobe emphysematous changes and lower-lobe reticular and fibrotic changes is not consistent with the airspace opacities found in AIP.

Desquamative interstitial pneumonia (**Option C**), a relatively severe form of smoking-related diffuse parenchymal lung disease, may also present with progressive dyspnea and cough. However, CT scans of a patient with desquamative interstitial pneumonia would reveal diffuse ground-glass opacification with lower-lobe predominance, which is not present in this patient's imaging studies.



ITEM 5

The clinical presentation of IPF (**Option D**) can mimic CPFE. However, pulmonary function tests manifest a pure restrictive pattern. A confident diagnosis can be made based on the presence of a usual interstitial pneumonia pattern on HRCT of the chest in the right clinical setting. In this patient, the presence of upper-lobe emphysema, in addition to lower-lobe fibrotic changes, confirms CPFE rather than IPF as the diagnosis.

KEY POINT

- Combined pulmonary fibrosis and emphysema (CPFE) is a distinct clinical entity in which fibrotic lung disease (lower lobe), similar to idiopathic pulmonary fibrosis, coexists with emphysematous changes (upper lobe) in the same patient.

Bibliography

Amariei DE, Dodia N, Deepak J, et al. Combined pulmonary fibrosis and emphysema: pulmonary function testing and a pathophysiology perspective. Medicina (Kaunas). 2019;55. [PMID: 31509942] doi:10.3390/medicina55090580

Item 6 Answer: A

Educational Objective: Treat mild persistent asthma with combination airway dilator and inhaled glucocorticoid.

The most appropriate management for this patient is to add beclomethasone dipropionate with albuterol (**Option A**) during asthma symptoms. The patient has persistent asthma defined by use of her short-acting β_2-agonist (albuterol) more than two times weekly but not more than once per day. She has no comorbidities or risk factors for severe exacerbation. Based on studies demonstrating that as-needed use of inhaled glucocorticoids in combination with airway dilators is noninferior to daily use of glucocorticoids and superior to short-acting β_2-agonists alone, the 2020 Global Initiative for Asthma guidelines recommend that patients with mild persistent asthma use an inhaled glucocorticoid whenever they use an inhaled short-acting β_2-agonist to reduce the risk of serious exacerbations and to control symptoms. An alternative is the inhaler combination of low-dose glucocorticoid-formoterol taken as needed for symptom relief. The National Asthma Education and Prevention Program also recommends an inhaled glucocorticoid, either as a daily low-dose inhaled glucocorticoid plus as-needed short-acting β_2-agonist or as-needed concomitant inhaled glucocorticoid and short-acting β_2-agonist. In addition to assessing symptom control, modifiable risk factors, and comorbidities, clinicians should review correct inhaler use with patients at each visit.

Bronchial challenge testing with methacholine (**Option B**) is used to identify bronchial hyperresponsiveness, a diagnostic feature of asthma. This is particularly helpful in patients whose symptoms are suggestive of asthma but for whom other pulmonary function test results are normal. A negative response to bronchial challenge can exclude asthma; however, a positive test can be caused by other conditions. Performing methacholine challenge testing is not appropriate because the patient's diagnosis of asthma has already been established with spirometry.

Montelukast (**Option C**) is an oral leukotriene-receptor antagonist that has a modest bronchodilation effect and can also treat upper airway conditions such as allergic rhinitis. Patients with aspirin-exacerbated respiratory disease often respond well to montelukast. Adding montelukast is not appropriate because the use of a daily medication is not recommended for intermittent asthma symptoms.

Not changing this patient's management (**Option D**) is not appropriate because the use of short-acting β_2-agonists without an inhaled glucocorticoid does not reduce exacerbation risk.

KEY POINTS

- Guidelines recommend that patients with mild persistent asthma use inhaled glucocorticoids whenever an inhaled short-acting β_2-agonist is used to reduce the risk of serious exacerbations and to control symptoms.
- Clinicians should review correct inhaler use with patients who have airways disease at each visit.

Bibliography

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: ginasthma.org/wp-content/uploads/2021/04/GINA-2021-Main-Report_FINAL_21_04_28-WMS.pdf. Accessed May 5, 2021.

Item 7 Answer: E

Educational Objective: Evaluate a small pulmonary nodule in a patient at low risk for malignancy.

The most appropriate next step in management is no further follow-up (**Option E**). Pulmonary nodules appear on radiography as small radiographic opacities (<3 cm in size) surrounded by normal lung parenchyma. These nodules are asymptomatic and are found either incidentally or on screening. In contrast, a focal pulmonary opacity larger than 3 cm is considered a lung mass and is presumed malignant until proved otherwise. This patient presents for evaluation of an incidentally found solid solitary pulmonary nodule. The first step in evaluation of a solitary pulmonary nodule is to determine likelihood of malignancy according to clinical and radiographic features. The risk can be considered low, intermediate, or high. This risk can be determined clinically or with quantitative prediction models such as the Brock University Lung Cancer Risk Calculators (brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/). Factors that help predict malignancy include smoking history, age, sex (female sex is associated with greater risk than male), family history of lung cancer, emphysema, asbestos exposure, size of the nodule, location (upper lobe is associated with greater risk than is lower lobe), and nodule type. It is also important to review older scans to determine whether the nodule has grown over time. In patients who have a low risk for malignancy, like this patient, a nodule (solid or subsolid) that is smaller than 6 mm requires no further follow-up.

Biopsy can be considered for an intermediate-risk nodule. A biopsy is not indicated in this patient who is at low risk for malignancy. If a biopsy is indicated, bronchoscopy (**Option A**) is typically used for lesions that are larger and more central; CT-guided needle biopsy (**Option C**) is used for smaller and more peripheral lesions.

In patients who are at high risk, optional follow-up CT (**Option B**) could be performed at 12 months; however, even in this group, the risk for malignancy in a nodule smaller than 6 mm is less than 1%.

Fluorodeoxyglucose PET (**Option D**) would not be helpful because it does not accurately characterize lesions that are less than 8 mm.

KEY POINTS

- The first step in evaluation of a solitary pulmonary nodule is to determine the likelihood of malignancy according to clinical and radiographic features.
- In patients who have a low risk for malignancy, a nodule that is smaller than 6 mm in size requires no further follow-up.

Bibliography

MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

Item 8 Answer: B

Educational Objective: Treat COPD with a long-acting bronchodilator.

The most appropriate treatment is inhaled tiotropium bromide (**Option B**). This patient's pulmonary disease is consistent with COPD. He has a chronic cough and dyspnea on exertion, a significant smoking history, a chest radiograph showing hyperinflation, and spirometry results demonstrating nonreversible obstruction. Pharmacologic therapies can be used to reduce symptoms, improve quality of life, and reduce exacerbations in patients with COPD. Regardless of COPD severity, bronchodilators are the mainstay of COPD therapy. Inhaled bronchodilators include β_2-agonists and antimuscarinic agents. There are inhaled short- and long-acting forms of both types. Initial management includes short-acting bronchodilators, but a long-acting β_2-agonist (LABA) or a long-acting muscarinic antagonist (LAMA), such as tiotropium bromide, should be added if symptoms are still poorly controlled. A combination LABA–LAMA can be used if patients have persistent symptoms despite monotherapy with either long-acting bronchodilator.

Inhaled glucocorticoids (**Option A**) can be used in combination with a bronchodilator in COPD but should not be used as monotherapy unless the patient cannot use a bronchodilator. A combination inhaled glucocorticoid–LABA could be considered if the patient's symptoms are poorly controlled with LABA or LAMA monotherapy, but that approach has not yet been tried in this patient.

Evidence-based guidelines do not endorse chronic oral glucocorticoid therapy with agents such as prednisone (**Option C**) because clinical trials have not shown improved outcomes with oral glucocorticoid therapy. In addition, there is ample evidence that chronic oral glucocorticoid therapy has potential for harm, including but not limited to hypertension, hyperglycemia, osteoporosis, and susceptibility to infection. Oral glucocorticoids are recommended for short-duration treatment of acute exacerbations of COPD.

Roflumilast (**Option D**), a selective phosphodiesterase-4 inhibitor, can reduce symptoms and exacerbations in patients with COPD who have chronic bronchitis or frequent exacerbations; thus, it is not the initial therapy of choice in this patient who lacks the sputum production of chronic bronchitis or history of frequent exacerbations.

KEY POINTS

- Regardless of COPD severity, β_2-agonists and anticholinergic/antimuscarinic agents are the mainstay of therapy.
- Initial management of COPD includes short-acting bronchodilators, but a long-acting β_2-agonist or long-acting muscarinic antagonist should be added if symptoms remain poorly controlled.

Bibliography

Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020; 201:e56-e69. [PMID: 32283960] doi:10.1164/rccm.202003-0625ST

Item 9 Answer: A

Educational Objective: Assess thermal upper airway injury with bronchoscopy.

The most appropriate next step is to perform bronchoscopy (**Option A**). This patient sustained thermal injury to his upper airway as evidenced by symptoms of tracheal irritation, sore throat, dysphonia, and an edematous oropharynx. Intense heat can cause edema and blistering from the mouth to the larynx, and patients with a visibly damaged airway or stridor are at high risk of complete upper airway obstruction due to swelling. It is difficult to predict which patients with acute inhalational injury will develop complete upper airway obstruction, and even patients with minimally apparent inhalational airway injury may develop worsening obstruction associated with intravenous hydration or analgesia needed for burn treatment. Following smoke inhalation, one third of patients develop airway edema or mucosal sloughing from epithelial necrosis. Chest physiotherapy and serial bronchoscopy are frequently necessary to facilitate continued airway clearance. Other presenting symptoms and signs of inhalation injury include stridor, dysphagia, singed nasal hairs, and sooty sputum, which signal the need

CONT.

for inspection of the upper airway. Immediate protection of the airway is indicated for patients with extensive facial or neck burns, decreased level of consciousness, or airway obstruction. If there is any doubt about the airway patency, intubation is always preferred.

Methylprednisolone (**Option B**) or other glucocorticoids do not have a role in treating upper airway edema or smoke-induced injury of the lower airways.

Nebulized epinephrine (**Option C**) can transiently reduce upper airway edema from allergic or anaphylactic reactions, but it does not have a role in the treatment of inhalational injury.

Noninvasive positive pressure ventilation (**Option D**) will not prevent this patient from developing progressive airway obstruction or clear the airway of debris.

KEY POINTS

- Following smoke inhalational injury, immediate protection of the airway is indicated for patients with extensive facial or neck burns, decreased level of consciousness, or airway obstruction.
- Following smoke inhalation, one third of patients develop airway edema or mucosal sloughing from epithelial necrosis; airway inspection, bronchoscopy, and chest physiotherapy are frequently necessary to facilitate continued airway clearance.

Bibliography

Sheridan RL. Fire-related inhalation injury. N Engl J Med. 2016;375:464-9. [PMID: 27518664] doi:10.1056/NEJMra1601128

Item 10 Answer: D

Educational Objective: Diagnose chronic thromboembolic pulmonary hypertension.

The most appropriate diagnostic test is ventilation/perfusion (V/Q) scanning (**Option D**) to screen for chronic thromboembolic pulmonary hypertension (CTEPH). The diagnosis of CTEPH is difficult and can be overlooked as a cause of pulmonary hypertension (PH). In patients diagnosed with PH, evaluation for CTEPH is warranted even when a history of acute pulmonary embolism is absent. The incidence of CTEPH following acute pulmonary embolism is likely less than 5%. More than 20% of patients with CTEPH do not have a previous diagnosis of pulmonary embolism. Therefore, the diagnosis of CTEPH should not automatically be excluded in patients without a history of pulmonary embolism. In patients who develop or continue to have symptoms suggesting PH after 3 months of appropriate anticoagulation for pulmonary embolism, screening for CTEPH is warranted. A normal V/Q scan is sufficient to exclude CTEPH as its sensitivity for detecting chronic thrombus approaches 100%. An abnormal V/Q requires additional investigation, typically with right heart catheterization and pulmonary angiography.

CT angiography (CTA) of the chest (**Option A**) is capable of detecting chronic thromboembolic material within dilated central pulmonary arteries but is less sensitive than pulmonary angiography or V/Q scanning in detecting CTEPH.

D-dimer (**Option B**) is useful for evaluating patients with suspected acute pulmonary embolism, but it has no utility in the evaluation of patients for CTEPH. This patient is taking apixaban and therefore is at very low risk for acute pulmonary embolism. In addition, his symptoms are progressive in nature, supporting a chronic condition over a recurrent thromboembolic event.

For patients with suspected CTEPH and an abnormal V/Q lung scan, right heart catheterization and pulmonary angiography (**Option C**) will confirm pulmonary hypertension, exclude competing diagnoses, and provide vital information related to potential therapy. Right heart catheterization and pulmonary angiography can be avoided in patients with a normal V/Q scan, and they should not be used as the initial tests in patients with suspected CTEPH.

KEY POINTS

- A ventilation/perfusion scan is recommended for all patients with pulmonary hypertension to rule out chronic thromboembolic pulmonary hypertension.
- For patients with suspected chronic thromboembolic pulmonary hypertension and an abnormal ventilation/perfusion scan, right heart catheterization and pulmonary angiography will confirm pulmonary hypertension, exclude competing diagnoses, and provide vital information related to potential therapy.

Bibliography

Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53. [PMID: 30545969] doi:10.1183/13993003.01915-2018

Item 11 Answer: B

Educational Objective: Treat COPD-related hypoxemia with supplemental oxygen therapy.

The most appropriate additional therapy is supplemental oxygen (**Option B**). The use of supplemental oxygen has been shown to improve quality of life and decrease mortality in patients with COPD and resting hypoxemia with an arterial $\mathrm{Po_2}$ of 55 mm Hg (7.3 kPa) or less, or oxygen saturation as measured by pulse oximetry of 88% or less. Patients with cor pulmonale, heart failure, or erythrocytosis should be offered the use of supplemental oxygen if $\mathrm{Po_2}$ is 59 mm Hg (7.8 kPa) or less or oxygen saturation is 89% or less. Some patients may not qualify for oxygen at rest but may desaturate during sleep, exertion, or air travel. Supplemental oxygen is typically prescribed if the oxygen saturation as measured by pulse oximetry falls below 89% in these patients, but the benefits are less defined.

Once a patient is started on long-term oxygen therapy, they should be re-evaluated after 2 to 3 months with a repeat arterial blood gas or oxygen saturation measurement to determine if the level of supplemental oxygen is therapeutic and if it is still indicated.

CONT.

The methylxanthines (aminophylline and theophylline) (**Option A**) are now rarely used to treat COPD. Theophylline has been shown to improve functional capacity and reduce the number of exacerbations; however, it has a narrow window between therapeutic and toxic dosages. Therefore it is used only for patients with advanced COPD who have refractory symptoms not controlled with standard therapy.

Adding home noninvasive positive pressure ventilation (**Option C**) to oxygen therapy in patients with persistent hypercapnia after an acute exacerbation of COPD prolongs the time to readmission and death. This patient does not have persistent hypercapnia and the use of noninvasive positive pressure ventilation is not indicated at this time.

Inhaled glucocorticoids (**Option D**) are typically used only in combination with a long-acting bronchodilator, not as monotherapy, for treatment of COPD. Inhaled glucocorticoids with bronchodilator therapy may improve lung function and reduce symptoms and exacerbations in patients with moderate to severe COPD, but they are associated with an increased risk of pneumonia.

KEY POINTS

- The use of supplemental oxygen has been shown to improve quality of life and decrease mortality in patients with COPD and resting hypoxemia with an arterial Po_2 of 55 mm Hg (7.3 kPa) or less, or oxygen saturation as measured by pulse oximetry of 88% or less.
- Patients with cor pulmonale, heart failure, or erythrocytosis should be offered the use of supplemental oxygen if Po_2 is 59 mm Hg (7.8 kPa) or less or oxygen saturation is 89% or less.

Bibliography

Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. N Engl J Med. 2019;381:1257-1266. [PMID: 31553837] doi:10.1056/NEJMra1900500

Item 12 Answer: B

Educational Objective: Evaluate patients with shock using point-of-care ultrasonography.

The most appropriate next step in management of shock in this patient is to perform chest ultrasonography (**Option B**). Possible reasons for this patient's sudden hypotension include procedure-related hemothorax and tension pneumothorax. In patients in shock, point-of-care lung ultrasonography can help rapidly assess patients for pneumothorax and pleural fluid. Point-of-care ultrasonography when placing central venous catheters is associated with reduced periprocedural complications, including bleeding and pneumothorax. However, these complications still occur. In this patient, rapid onset of hypotension and poor lung and heart sounds should prompt the clinician to evaluate for intrathoracic bleeding or pneumothorax. The clinician can do so using point-of-care ultrasonography. In addition, lung ultrasonography can quickly visualize very small amounts of fluid within the pleural space.

Chest CT (**Option A**) would confirm whether a patient has a pneumothorax or pleural effusion. However, delays associated with obtaining chest CT as well as the need to transport the patient to a CT scanner pose additional clinical risk to this unstable patient. Alternative measures that can be done quickly at the bedside are indicated to assess for periprocedural complications.

Needle thoracostomy (**Option C**) can help reverse the hemodynamic impact of a tension pneumothorax and often serves as a temporizing measure until a thoracostomy is placed. However, this maneuver is associated with risk, including intercostal or pulmonary vascular injury, intercostal nerve injury, and cardiac puncture or tamponade. In addition, if tension pneumothorax is not the cause of the hypotension, the patient would unnecessarily need a thoracostomy to re-expand the lung. It is not clear whether tension pneumothorax has caused this patient's hypotension, especially given that breath sounds are diminished on both sides. Needle thoracostomy should not be performed without first establishing the diagnosis of pneumothorax.

Pneumothorax and vascular injury may occur during needle placement. It is rarely caused by the presence of the vascular catheter itself. Thus, removing the central venous catheter (**Option D**) would not address the patient's hypotension. It is reasonable to keep the catheter in place while investigating the cause of the patient's hypotension.

KEY POINTS

- Possible reasons for sudden hypotension following central line insertion include procedure-related hemothorax and tension pneumothorax.
- Point-of-care lung ultrasonography can help rapidly assess patients for pneumothorax and pleural fluid.

Bibliography

Parulekar P, Harris T, Jarman R. The use of lung ultrasound in acute medicine. Acute Med. 2019;18:239-246. [PMID: 31912055]

Item 13 Answer: A

Educational Objective: Treat mild persistent asthma by stepping up therapy.

The most appropriate treatment is to step up therapy by adding a long-acting β_2-agonist (LABA) to the current inhaled glucocorticoid (**Option A**); the preferred method would be by starting a combined budesonide-formoterol inhaler. This patient has mild persistent asthma with low-dose inhaled glucocorticoid maintenance therapy and now has increasing symptoms requiring frequent use of her short-acting β_2-agonist (SABA) inhaler. A step up in therapy is indicated for inadequate asthma control, including either use of a SABA more than twice weekly (not related to prevention of exercise-induced bronchospasm) or need for a SABA two or more times monthly for nocturnal symptoms. Guidelines indicate that the preferred next step is combined therapy with a low-dose inhaled glucocorticoid and LABA in a single inhaler. When LABAs are added to inhaled glucocorticoids, they provide improved control and decrease the risk of exacerbations. Administration in a single inhaler is preferred because it improves adherence and may reduce cost compared with administration of each drug in a separate inhaler. Other treatment options would include increasing the patient's regimen to a medium-dose inhaled glucocorticoid or adding a leukotriene receptor antagonist to her current dose of an inhaled glucocorticoid.

Azithromycin (**Option B**) can be used to treat upper and lower respiratory tract infections and is also recommended as add-on therapy given three times weekly for persistent asthma not controlled by combined moderate- to high-dose inhaled glucocorticoids with LABA. However, this patient does not have symptoms that suggest infection and has not yet had a trial of combined inhaled glucocorticoid–LABA therapy, making this choice incorrect.

Use of prednisone (**Option C**) could be considered if the patient does not improve with a step up in her maintenance therapy or if her clinical symptoms become more severe. However, this would not be recommended as the initial choice.

Long-acting muscarinic antagonists (LAMAs) such as tiotropium (**Option D**) provide sustained airway dilation. When added to therapy for asthma not controlled with inhaled glucocorticoid–LABA combination therapy, tiotropium has been shown to improve lung function and reduce exacerbations. However, no substantial evidence shows that LAMAs should be the first choice for long-acting airway dilation, and National Asthma Education and Prevention Program guidelines specifically advise against using a LAMA as the initial agent to step up from inhaled glucocorticoid controller therapy.

KEY POINTS

- The preferred next step for patients with inadequately controlled mild persistent asthma on an inhaled glucocorticoid is combined therapy with a low-dose inhaled glucocorticoid and long-acting β_2-agonist in a single inhaler.
- Administration of a glucocorticoid and long-acting β_2-agonist in a single inhaler is preferred because it improves adherence and may reduce cost compared with administration of each drug in a separate inhaler.

Bibliography

Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA. 2020;324:2301-2317. [PMID: 33270095] doi:10.1001/jama.2020.21974

Item 14 Answer: B

Educational Objective: Prevent COPD exacerbations with long-term azithromycin therapy.

Addition of azithromycin (**Option B**) may help decrease the frequency of this patient's COPD exacerbations. The patient's medications are a combination inhaled glucocorticoid, a long-acting β_2-agonist, and a long-acting antimuscarinic agent, as well as albuterol as needed. Macrolide antibiotics (e.g., azithromycin) have both inflammatory and antimicrobial effects. Long-term macrolide therapy reduces the frequency of exacerbations in patients with severe COPD and a history of frequent exacerbations. The major concern regarding long-term macrolide therapy is QT prolongation, but the risk for cardiovascular death associated with long-term azithromycin therapy is low (1 in 20,000) for patients without cardiac disease. Other standard interventions to reduce COPD exacerbations include smoking cessation, proper immunizations, and pulmonary rehabilitation programs. Roflumilast, a selective phosphodiesterase-4 inhibitor, can also be used for patients with COPD and frequent exacerbations. There are no head-to-head comparisons of roflumilast with azithromycin. The choice of medication is determined by the medication's side effects, drug interactions, and contraindications.

Antiproteases, including α_1-antitrypsin (**Option A**), typically inactivate proteases that may lead to permanent lung injury. In patients with α_1-antitrypsin deficiency, replacing this enzyme with augmentation therapy may slow the progression of related emphysema. However, it is costly, does not decrease exacerbations or the rate of FEV_1 decline, and is not effective for treatment of patients whose COPD is not caused by α_1-antitrypsin deficiency.

Early observational studies suggested that metoprolol (**Option C**) used by patients with COPD and cardiovascular disease might be responsible for a reduction in COPD exacerbations. A randomized study showed the reverse, with more patients in the metoprolol arm hospitalized for acute COPD exacerbation. There were no between-group differences in forced expiratory volume in 1 second (FEV_1), and the cause of the increased rate of COPD exacerbations remains unknown.

Mucolytic agents such as oral *N*-acetylcysteine (**Option D**) may relieve symptoms in patients who produce large volumes of sputum but have not been shown to decrease the frequency of COPD exacerbations. This patient has thin secretions and will not benefit from *N*-acetylcysteine.

KEY POINT

- Long-term macrolide therapy reduces the frequency of exacerbations in patients with severe COPD and a history of frequent exacerbations.

Bibliography

Vermeersch K, Gabrovska M, Aumann J, et al. Azithromycin during acute chronic obstructive pulmonary disease exacerbations requiring hospitalization (BACE). A multicenter, randomized, double-blind, placebo-controlled trial. Am J Respir Crit Care Med. 2019;200:857-868. [PMID: 31046405] doi:10.1164/rccm.201901-0094OC

Item 15 Answer: B

Educational Objective: Treat recurrent symptomatic malignant pleural effusion with an indwelling pleural catheter.

The most appropriate management for this patient is placement of an indwelling pleural catheter (IPC) (**Option B**). The diagnosis of a malignant pleural effusion signifies advanced

H CONT.

disease and overall poor prognosis (usually 4-7 months from the time of diagnosis). In these patients, the goal of management is relief of symptoms. Several therapeutic options exist, and treatment decisions should be based on symptoms, prognosis, degree of anticipated lung re-expansion, and patient performance status. The patient has a recurrent symptomatic malignant pleural effusion that requires definitive management given the rapidity of recurrence. Initial treatment choices include IPC and chemical pleurodesis with talc, and either may be used as first-line treatment in patients with expandable lung. In this patient, however, because there is evidence of incomplete lung expansion on his post-thoracentesis radiographs, the treatment of choice is IPC. Incomplete expansion of the lung is common in malignant pleural effusion. It is diagnosed with either pleural manometry (measurement of intrapleural pressures during a thoracentesis) or, as in this patient, evidence of incomplete re-expansion (air replacing the drained pleural effusion) on a post-thoracentesis chest radiograph. Nonexpandable lung has a variety of causes, including pleural thickening, pleural tumor, septations, loculations, and endobronchial obstruction.

Chemical pleurodesis (**Option A**) refers to obliteration of the pleural space with a sclerosing agent, typically talc. Talc can be introduced through a thoracostomy tube (talc slurry) or during a thoracoscopy (talc poudrage). Successful pleurodesis requires apposition of the parietal and visceral pleural surfaces, which limits the use of this treatment in patients with an unexpanded lung.

Repeat therapeutic thoracentesis (**Option C**) is appropriate for patients with poor prognosis (<3 months) and slow reaccumulation of fluid. It would not be the best choice for this patient because of the rapidity of symptomatic fluid reaccumulation.

Surgical decortication (**Option D**) is not used as first-line treatment for recurrent malignant pleural effusion because of its associated costs and morbidity.

KEY POINTS

- Initial treatment of a malignant pleural effusion in patients with expandable lung includes either an indwelling pulmonary catheter or chemical pleurodesis with talc.
- In patients with a malignant pleural effusion and a nonexpanding lung, an indwelling pulmonary catheter is the treatment of choice.

Bibliography

Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of malignant pleural effusions. an official ATS/STS/STR clinical practice guideline. Am J Respir Crit Care Med. 2018;198:839-849. [PMID: 30272503] doi:10.1164/rccm.201807-1415ST

Item 16 Answer: D

Educational Objective: Manage asymptomatic stage I pulmonary sarcoidosis.

The most appropriate management for this patient is observation (**Option D**). The patient most likely has stage I pulmonary sarcoidosis, a granulomatous disease of unknown cause that can affect any organ system but most commonly affects the lungs. Sarcoidosis affects Blacks more frequently than Whites and typically occurs in younger patients. Many patients are asymptomatic, and lung involvement is found incidentally on a chest radiograph obtained for other reasons. Pulmonary sarcoidosis is classified into four stages based on appearance on chest radiograph: stage I, bilateral hilar lymphadenopathy; stage II, bilateral hilar lymphadenopathy with pulmonary infiltrates; stage III, parenchymal infiltrates alone; and stage IV, pulmonary fibrosis with parenchymal distortion or bullae. For patients with stage I disease, clinical diagnosis based on a classic presentation is a cost-effective strategy, with pretest probability approaching 99.95%. The overall prognosis of stage I pulmonary sarcoidosis is excellent, with spontaneous regression of radiographic abnormalities observed in most patients.

Diagnosis of pulmonary sarcoidosis, with a few exceptions, typically requires bronchoscopic biopsy (**Option A**), with tissue obtained from a lymph node or from the pulmonary parenchyma. The diagnosis is made by the finding of noncaseating granulomas with exclusion of potential mimicking infections (mycobacteria, fungi), exclusion of other systemic granulomatous diseases, and involvement of more than one organ system. The absence of respiratory and constitutional symptoms makes infectious and malignant causes unlikely. Clinical presentations of sarcoidosis that do not require a biopsy include asymptomatic stage I pulmonary sarcoidosis (absence of fevers, malaise, or night sweats to suggest a malignancy); Löfgren syndrome (bilateral hilar lymphadenopathy, migratory polyarthralgia, erythema nodosum, and fever); and Heerfordt syndrome (anterior uveitis, parotiditis, fever, and facial nerve palsy). This asymptomatic patient with stage I pulmonary sarcoidosis does not need a bronchoscopic biopsy.

The primary treatment for symptomatic pulmonary sarcoidosis is systemic glucocorticoids. Methotrexate (**Option B**) may be used for patients who cannot tolerate glucocorticoids due to adverse effects or those who continue to have disabling symptoms despite glucocorticoid treatment. Methotrexate may also be used as a glucocorticoid-sparing therapy to limit adverse effects from long-term use of glucocorticoids. Neither glucocorticoids nor methotrexate is indicated for asymptomatic stage I pulmonary sarcoidosis.

Glucocorticoids, typically prednisone (**Option C**), are the mainstay of therapy for sarcoidosis. However, initial treatment is usually limited to symptomatic patients with pulmonary/extrapulmonary organ dysfunction. Patients who require long-term glucocorticoids are frequently transitioned to glucocorticoid-sparing agents such as methotrexate or leflunomide. Treatment with prednisone would not be the most appropriate initial treatment for this asymptomatic patient with stage I disease.

KEY POINTS

- Clinical presentations of sarcoidosis that do not require a biopsy include asymptomatic stage I pulmonary sarcoidosis, Löfgren syndrome, and Heerfordt syndrome.

(Continued)

KEY POINTS *(continued)*

- The overall prognosis of stage I pulmonary sarcoidosis is excellent, with spontaneous regression of radiographic abnormalities observed in most patients.

Bibliography

Ungprasert P, Ryu JH, Matteson EL. Clinical manifestations, diagnosis, and treatment of sarcoidosis. Mayo Clin Proc Innov Qual Outcomes. 2019;3:358-375. [PMID: 31485575] doi:10.1016/j.mayocpiqo.2019.04.006

Item 17 Answer: D

Educational Objective: Diagnose asthma with bronchial challenge testing.

The most appropriate management for this patient is methacholine challenge testing (**Option D**). Confirmation of reversible airflow obstruction is a cornerstone of asthma diagnosis, and spirometry should be performed on all patients with suspected asthma. For some patients, however, airflow obstruction is not present during the initial spirometry, and a bronchial challenge test is indicated to evaluate for bronchial hyperreactivity, which supports an asthma diagnosis. The test is usually performed with inhaled methacholine, although other stimuli (exercise, mannitol) also have been validated. Bronchial challenge tests measure spirometry following a controlled inhaled stimulus; a positive test is indicated by a drop in the measured FEV_1. If the result is negative, it is unlikely that the patient has asthma, but a positive result in isolation is not specific enough to diagnose asthma. Therefore, to confirm the diagnosis, patients with a positive methacholine challenge test and suggestive asthma symptoms must also respond clinically to treatment with asthma therapies. This patient's typical symptoms and improvement with standard asthma therapy would indicate asthma if the methacholine challenge test result were positive.

Although initiating a trial of asthma treatment with budesonide-salmeterol or fluticasone (**Options A, B**) could be considered, guidelines indicate that it is preferable to first establish a diagnosis to avoid prescribing unnecessary or incorrect treatment. It is more difficult to establish the diagnosis of asthma once the patient is taking controller medications.

Measurement of the fractional exhaled nitric oxide (FeNO) (**Option C**) in an exhaled breath sample provides a noninvasive way to quantify eosinophilic airway inflammation and serves as a complementary tool in the management of lung diseases, in particular, asthma. However, the role of FeNO in the diagnosis of asthma has not been established. Although an elevated FeNO is characteristic of type 2 airway inflammation, FeNO is also elevated in disorders such as eosinophilic bronchitis, atopy, and allergic rhinitis and is not elevated in some asthma phenotypes. Spirometry remains the first test of choice to diagnose asthma.

KEY POINTS

- For patients with asthma symptoms and a normal spirometry, a positive bronchial challenge test followed by relief of symptoms with standard asthma therapy confirms the diagnosis of asthma.
- A negative bronchial challenge test excludes the diagnosis of asthma in most patients.

Bibliography

Coates AL, Wanger J, Cockcroft DW, et al; Bronchoprovocation Testing Task Force: Kai-Håkon Carlsen. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J. 2017;49. [PMID: 28461290] doi:10.1183/13993003.01526-2016

Item 18 Answer: C

Educational Objective: Treat neutropenic sepsis with an appropriate duration of antibiotic therapy.

No change in treatment (**Option C**) is most appropriate for this patient. In patients with neutropenic fever, it is always appropriate to provide empiric gram-positive and gram-negative coverage as an initial approach. Coverage for methicillin-resistant *Staphylococcus aureus* should be considered if the patient is hemodynamically unstable, but it can be discontinued after 2 to 3 days if culture data are unrevealing. Notation of previous infections, resistance patterns, and local antibiograms should guide decisions on the initial regimen, although carbapenems or extended-range penicillin–β-lactamase inhibitors are a reasonable empiric choice for most patients. Most neutropenic fevers have no known source. In situations in which no pathogen is identified, antibiotic discontinuation is largely contingent on two criteria: resolution of fever and improvement of the patient's absolute neutrophil count to more than 500/µL (0.5×10^9/L).

Indications for modifying a patient's antibiotic coverage include identification of an infectious source, escalation of therapy for persistent fever or worsening clinical status, and, in some cases, transition to an oral regimen for patients leaving the hospital. Because this patient does not meet any of these criteria, switching from piperacillin-tazobactam to imipenem-cilastatin (**Option A**) would not be indicated.

This patient is hemodynamically stable, appears clinically improved, and is afebrile, but the absolute neutrophil count has not recovered. Antibiotics should be continued until either the absolute neutrophil count recovers or the patient has completed a full course of antibiotic therapy, whichever is longest. Some guidelines suggest discontinuing antibiotics after 48 to 72 hours in patients without fever who are improving and have no clear source for infection, regardless of neutrophil recovery. Because this patient has been afebrile for only 24 hours and her absolute neutrophil count has not recovered, it would not be appropriate to discontinue antibiotics (**Option B**) at this time.

The risk of fungemia is increased in patients who remain neutropenic and febrile for more than 7 days. If a patient remains febrile for more than 4 days, addition of an

CONT.

antifungal agent such as voriconazole (**Option D**) is warranted if the patient's neutropenia is expected to last beyond 7 days and no alternative source for the infection has been identified. Because this patient is no longer febrile, addition of an antifungal agent is not indicated.

KEY POINT

- In patients with neutropenic fever, antibiotics should usually be continued until either the absolute neutrophil count recovers (>500/µL [0.5×10^9/L]) or the patient has completed a full course of antibiotic therapy, whichever is longest.

Bibliography

Cantwell L, Perkins J. Infectious disease emergencies in oncology patients. Emerg Med Clin North Am. 2018;36:795-810. [PMID: 30297005] doi:10.1016/j.emc.2018.06.009

Item 19 Answer: B

Educational Objective: **Treat neuroleptic malignant syndrome.**

The most appropriate initial treatment is discontinuation of risperidone (**Option B**). This patient developed neuroleptic malignant syndrome as a result of risperidone (an atypical antipsychotic) and promethazine (an antiemetic agent). Neuroleptic malignant syndrome is characterized by fever, mental status changes, muscle rigidity, and dysautonomia. The syndrome is seen both with first-generation antipsychotics and with newer atypical antipsychotics and antiemetics. It is most common at times of medication initiation or escalation of medication doses. It can also be caused by rapid withdrawal of dopaminergic medications. In addition to discontinuation of the triggering agents, active cooling and supportive care (including intravenous fluids) may be used. The mortality rate associated with neuroleptic malignant syndrome may exceed 10%.

Serotonin syndrome is most commonly associated with the use of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (**Option A**) and is typically precipitated by the addition of a second medication that affects the release or uptake of serotonin. Serotonin syndrome is characterized by mental status changes, dysautonomia, hyperthermia, myoclonus, and hyperreflexia. The two features that are most helpful in distinguishing serotonin syndrome from neuroleptic malignant syndrome are the presence of hyperreflexia and myoclonus. Initial management includes removal of the offending agents and supportive care, including benzodiazepines.

Cyproheptadine (**Option C**) may also be used off-label for serotonin syndrome if symptoms persist despite benzodiazepines. Because this patient does not have serotonin syndrome, these medications are not appropriate.

Malignant hyperthermia is an autosomal dominant condition resulting from deranged intracellular calcium metabolism in response to inhaled anesthetic agents and succinylcholine. It is characterized by severe hyperthermia, muscle rigidity, rhabdomyolysis, and arrhythmias. Treatment includes cessation of the triggering agent, active cooling, and administration of dantrolene (**Option D**). This patient has not received agents known to trigger malignant hyperthermia, and the patient's symptoms are not consistent with this diagnosis.

KEY POINTS

- Neuroleptic malignant syndrome is characterized by fever, mental status changes, muscle rigidity, and dysautonomia and is seen with both first-generation antipsychotics and newer atypical antipsychotics and antiemetics.
- Treatment of neuroleptic malignant syndrome includes discontinuation of the triggering agent, active cooling, and supportive care.

Bibliography

Ware MR, Feller DB, Hall KL. Neuroleptic malignant syndrome: diagnosis and management. Prim Care Companion CNS Disord. 2018;20. [PMID: 29325237] doi:10.4088/PCC.17r02185

Item 20 Answer: D

Educational Objective: **Treat smoking-related diffuse parenchymal lung disease.**

This patient has smoking-related diffuse parenchymal lung disease (DPLD), and smoking cessation is the most appropriate treatment (**Option D**). There are several DPLDs that occur almost exclusively in persons who are current smokers. The pathology from smoking-related DPLD includes respiratory bronchiolitis–associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), pulmonary Langerhans cell histiocytosis (PLCH), and smoking-related interstitial fibrosis (SRIF). Smoking in conjunction with other endogenous or exogenous factors may also contribute to idiopathic pulmonary fibrosis as well as combined pulmonary fibrosis and emphysema. Physiologically, smoking-related DPLD may have obstructive, restrictive, or mixed defects. This patient has a restrictive defect. DLCO is reduced in all patients with DPLD, including smoking-related DPLD. Findings on high-resolution CT (HRCT) can often help distinguish between the various types of smoking-related DPLD. This patient's HRCT findings of lower-lobe-predominant ground-glass opacities suggest DIP. RB-ILD is characterized by patchy ground-glass opacities with fine centrilobular nodules. PLCH, in contrast, is characterized by diffuse thin-walled cysts and nodular lesions in the mid- and upper lung zones. SRIF mimics RB-ILD on chest radiograph; however, it is pathologically distinct, with deposition of hyalinized collagen in alveolar septa and minimal inflammation. For all smoking-related DPLDs, smoking cessation is the cornerstone of treatment. Patients should receive behavioral counseling and at least one of seven FDA-approved treatments for smoking cessation.

Glucocorticoids (**Option A**) may be required in severe disease or refractory cases of smoking-related DPLD, but they should not be instituted in the absence of smoking cessation.

Immunosuppressant therapies are occasionally used in selected patients with interstitial lung disease. Methotrexate (**Option B**) is not used and is not recommended for patients with DIP or other DPLDs. Methotrexate, particularly chronic low-dose methotrexate, is associated with a small but not insignificant risk of pulmonary toxicity, including hypersensitivity pneumonitis, organizing pneumonia, acute interstitial pneumonia, and pulmonary fibrosis.

Pirfenidone (**Option C**) is an antifibrotic agent that is FDA approved for the treatment of idiopathic pulmonary fibrosis. It does not have a role in the management of smoking-related DPLD in general or DIP specifically.

KEY POINTS

- There are several diffuse parenchymal lung diseases that occur almost exclusively in persons who are current smokers.
- For all smoking-related diffuse parenchymal lung diseases, smoking cessation is the cornerstone of treatment.

Bibliography

Kumar A, Cherian SV, Vassallo R, et al. Current concepts in pathogenesis, diagnosis, and management of smoking-related interstitial lung diseases. Chest. 2018;154:394-408. [PMID: 29222007] doi:10.1016/j.chest.2017.11.023

H Item 21 Answer: A

Educational Objective: Diagnose acute respiratory distress syndrome.

The most likely diagnosis is acute respiratory distress syndrome (ARDS) (**Option A**). The diagnosis of ARDS is based on the 2012 Berlin criteria: onset within 1 week of known ARDS insult (most are within 72 hours); bilateral opacities on chest imaging consistent with pulmonary edema; respiratory failure not related to cardiac failure or volume overload; arterial Po_2/Fio_2 ratio less than 300 on at least 5 cm H_2O positive end-expiratory pressure (PEEP). Once criteria are met, the severity of ARDS is based on the arterial Po_2/Fio_2 ratio: mild, >200 to <300; moderate, 100 to 200; severe, <100. This patient meets the diagnostic criteria for moderate ARDS. Her Po_2/Fio_2 ratio is 132. This patient likely has ARDS secondary to trauma.

Diffuse alveolar hemorrhage (**Option B**) is the result of bleeding into the alveolar spaces secondary to the disruption of the alveolar-capillary basement membrane. Most patients present with hemoptysis, although this might be absent and the diagnosis nevertheless suggested by the appearance of new diffuse or focal infiltrates and falling hemoglobin level. Considering the relationship of the trauma to the onset of respiratory distress and absence of hemoptysis, ARDS is a more likely diagnosis.

Acute cardiogenic pulmonary edema (**Option C**) can present as hypoxemic respiratory failure. In patients who present with acute respiratory failure, it is important to evaluate for cardiogenic causes. Evaluation should include an assessment for volume overload (jugular venous distention, S_3, peripheral edema), an ECG, echocardiography, and measurement of B-type natriuretic peptides and serial serum troponins. Although cardiac contusion can lead to heart failure from valvular injury or cardiac dysfunction, this patient does not have any evidence thus far to support the diagnosis of pulmonary edema.

Patients with pulmonary embolism (**Option D**) may present with chest pain, dyspnea, and tachypnea. Chest radiograph may demonstrate peripheral, wedge-shaped opacities, but most often the chest radiograph is normal. This patient's clinical course is most consistent with ARDS.

KEY POINT

- The diagnosis of acute respiratory distress syndrome (ARDS) is based on the onset of respiratory failure within 1 week of known ARDS insult; bilateral opacities on chest imaging consistent with pulmonary edema; respiratory failure not related to cardiac failure or volume overload; and arterial Po_2/Fio_2 ratio less than 300 on at least 5 cm H_2O positive end-expiratory pressure.

Bibliography

Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562-572. [PMID: 28792873] doi:10.1056/NEJMra1608077

Item 22 Answer: A

Educational Objective: Treat shift-work sleep disorder.

The most appropriate management is education and counseling (**Option A**). As much as one fifth of the American work force maintains a job schedule outside of usual day shift hours. Although some people acclimate well to this schedule, many experience excessive sleepiness, mood perturbations, and neurocognitive dysfunction. Symptoms persisting at least 3 months meet the criteria for shift work sleep disorder. Management should first include counseling that takes into consideration eliminating shift work. If this is not feasible, then education about symptom management should be pursued. This patient has difficulty falling asleep after her nighttime shift. Education on avoidance of direct sunlight in the early morning (using sunglasses or a dark bedroom) and avoidance of exertion, eating, and alcohol consumption before the morning sleep period should be provided. Daytime sleepiness may respond to use of caffeinated beverages, bright-light exposure during the work shift, and if feasible, a short (30-minute) nap, perhaps during a meal break.

Home sleep apnea testing (**Option B**), which uses respiratory tools and/or noninvasive measurements of vascular tone, pulse oximetry, and an accelerometer to detect posture, is indicated when there is strong pretest evidence of obstructive sleep apnea. The suspicion of obstructive sleep apnea in a young woman of normal weight is low; in addition, her main symptoms are difficulty falling asleep and associated daytime sleepiness. If the patient's symptoms persist after conservative therapy, in-laboratory polysomnography could be considered for a more comprehensive evaluation.

Modafinil (**Option C**), a novel stimulant, is approved to treat shift work sleep disorder. It should be considered only after conservative measures have failed. Modafinil is limited by cost and adverse effects, including headache, anxiety, and (rarely) serious skin reactions.

Hypnotic medications such as zolpidem (**Option D**) have been used to promote daytime sleep but are of varying effectiveness and pose a risk of carryover effects into the work period. Pharmacologic agents are considered second-line treatments to counseling, education, and other nonpharmacologic interventions.

KEY POINTS

- Conservative strategies for shift work sleep disorder to promote wakefulness include caffeinated beverages, bright-light exposure during the work shift, and short naps during breaks.
- Conservative strategies for shift work sleep disorder to promote sleep include avoidance of direct sunlight in the early morning and avoidance of exertion, eating, and alcohol consumption before the morning sleep period.

Bibliography

Reis C, Staats R, Pellegrino P, et al. The prevalence of excessive sleepiness is higher in shift workers than in patients with obstructive sleep apnea. J Sleep Res. 2020;29:e13073. [PMID: 32395904] doi:10.1111/jsr.13073

Item 23 Answer: A

Educational Objective: Diagnose asbestos-related lung disease.

The most likely occupational exposure is asbestos (**Option A**). The most likely diagnosis in this patient is malignant mesothelioma, an aggressive tumor arising from mesothelial cells. Malignant mesothelioma is associated with occupational asbestos exposure in up to 70% of cases. Patients can have a long latent period, extending into decades, before manifesting the disease. Therefore, it is essential to obtain a thorough employment history, including the use of respiratory protective equipment at the workplace. Patients usually present with chest pain, dyspnea, cough, and restrictive gas exchange abnormality. The radiographic manifestation is usually a unilateral pleural effusion or pleural thickening. CT is the primary modality for the diagnosis and staging of malignant mesothelioma. Prognosis is poor, with most patients dying of local extension of the disease and respiratory failure within 12 to 18 months of diagnosis.

Inhalation of coal dust (**Option B**) may result in coal worker's pneumoconiosis. Coal dust may contain high concentrations of silica and silicates, which can result in a rapidly progressive lung disease with imaging characteristics that include honeycombing and ground-glass opacification. Inhalation of coal dust without substantial amounts of silica can result in nodular opacities and eventually massive pulmonary fibrosis. These findings are currently less common because of improved mine safety standards. Pleural effusions are not commonly seen.

Inhalation of hard metal dusts can result in pneumoconiosis. Exposure to the hard metal cobalt (**Option C**) may occur during the processing of cobalt or the use of cobalt by diamond polishers. Cobalt exposure can result in accumulation of alveolar macrophages and multinucleated giant cells in the alveolar space, known as giant cell pneumonia. Chest imaging may show nodular and reticular opacities and small cystic spaces. Pleural effusions are uncommon.

Silicosis describes a spectrum of fibrotic lung disease that results from exposure to silica dust (**Option D**). Any occupation that disturbs the earth's crust involves potential risk. Workers in industries that cut or grind silica-containing materials, perform sandblasting, or conduct hydraulic fracking for natural gas are at risk. On chest imaging, the disease presents with ground-glass, nodular, interstitial, or fibrotic infiltrates. Pleural effusions are uncommon with silicosis.

KEY POINTS

- Malignant mesothelioma is associated with occupational asbestos exposure in up to 70% of cases; the radiographic manifestation is usually a unilateral pleural effusion or pleural thickening.
- Mesothelioma can have a long latent period, extending into decades after asbestos exposure; therefore, it is essential to obtain a thorough employment history.

Bibliography

Solbes E, Harper RW. Biological responses to asbestos inhalation and pathogenesis of asbestos-related benign and malignant disease. J Investig Med. 2018;66:721-727. [PMID: 29306869] doi:10.1136/jim-2017-000628

Item 24 Answer: A

Educational Objective: Diagnose allergic asthma phenotype.

The most appropriate diagnostic test for this patient is measurement of the absolute blood eosinophil count (**Option A**). The patient presents with symptoms suggestive of allergic asthma; establishing this asthma phenotype can help direct therapy. Clinical characteristics suggesting a type 2 asthma phenotype include atopy, seasonal exacerbations, hay fever, and allergen sensitization. Biomarker evaluation in these patients often demonstrates serum or sputum eosinophilia and/or high IgE levels. This patient has a normal IgE level, but this does not preclude type 2 asthma. Obtaining a blood absolute eosinophil count will help establish the phenotype. In patients with severe disease, elevated levels of IgE and eosinophils are therapeutic targets for biologic therapies. Several types of biologic therapies are available that are directed against type 2 inflammation, targeting pathways involved in activation of eosinophils and IgE production.

Use of antibody therapies in eligible patients with severe persistent allergic asthma despite standard therapy reduces symptoms, exacerbations, and need for oral glucocorticoids.

An α_1-antitrypsin level (**Option B**) should be obtained once in all patients with chronic obstructive pulmonary disease. A pattern of basilar emphysema, associated liver disease or panniculitis, or a strong family history of emphysema in patients with COPD suggests possible α-1 antitrypsin deficiency, but none of these features is sufficiently sensitive for the condition. Routine testing is not indicated in patients with asthma.

Patients with allergic bronchopulmonary aspergillosis (ABPA) present with difficult-to-control asthma, productive cough, and expectoration of mucus plugs. Commonly accepted diagnostic criteria include elevated IgE levels, positive skin tests to *Aspergillus* antigens, increased *Aspergillus*-specific IgE and IgG levels, and either central bronchiectasis or infiltrates. This patient does not have the clinical phenotype of ABPA, radiographic findings, or elevated IgE level suggesting ABPA. Measuring *Aspergillus*-specific IgE level (**Option C**) is not indicated.

Identifying the presence of atopy can identify an allergic asthma phenotype in a patient with respiratory symptoms. Atopic status can be measured by skin prick testing or measurement of allergen-specific IgE testing (**Option D**). Skin prick testing is rapid, simple, and relatively inexpensive. Measurement of immunoglobulin-specific IgE is more expensive but not more accurate. However, the first management step for this patient is to measure the total blood eosinophil count to determine his asthma phenotype.

KEY POINTS

- Clinical characteristics suggesting a type 2 asthma phenotype include atopy, seasonal exacerbations, hay fever, and allergen sensitization.
- For patients with symptoms suggestive of type 2 asthma phenotype, measurement of IgE levels and total eosinophil count can be used to confirm this asthma phenotype and direct therapy.

Bibliography

McGregor MC, Krings JG, Nair P, et al. Role of biologics in asthma. Am J Respir Crit Care Med. 2019;199:433-445. [PMID: 30525902] doi:10.1164/rccm.201810-1944CI

H

Item 25 Answer: D

Educational Objective: Evaluate occupational lung disease using the employer Safety Data Sheet.

The most appropriate next diagnostic step is review of the Safety Data Sheet (SDS) (**Option D**). The patient's history suggests a discrete temporal relationship to an accidental irritant exposure and onset of respiratory symptoms consistent with a diagnosis of reactive airways dysfunction syndrome. Reactive airways dysfunction syndrome is a well-described subset of irritant-induced occupational asthma. This syndrome occurs in patients without preexisting asthma following a single, high-level exposure to fumes, gases, or vapors. The diagnosis requires evidence of asthmatic symptoms for at least 3 months after the exposure and is confirmed by airway obstruction or bronchial hyperreactivity. The SDS includes information on the properties of each chemical on site, along with the physical, health, and environmental health hazards; protective measures; and safety precautions for handling, storing, and transporting the chemical. In the United States, the Occupational Safety and Health Administration requires employers to make this information available upon request for employees who work with potentially harmful chemicals. Cleaning products contain volatile chemicals, and acute and chronic inhalation exposures pose respiratory health risks, including asthma. A list of agents that can cause occupational asthma is available at: www.cdc.gov/niosh/topics/asthma/exposures.html.

If the patient's symptoms become chronic and occupational asthma is strongly suspected, a combination of objective evidence of asthma with specific immunologic or skin prick testing (**Option A**) for the suspected agent, when available, has a high predictive value for diagnosis. Additional tests to evaluate for occupational respiratory illnesses may include bronchoprovocation testing and, in select patients, specific inhalational challenges.

Bronchoscopy (**Option B**) does not have a role in the diagnosis of reactive airways dysfunction syndrome. It may be considered if the clinical picture is atypical with concerns for pneumonia or alveolitis. However, it would not precede a review of the SDS whenever an occupational lung disease is suspected.

In patients with clinical symptoms suggestive of bronchospastic disease but with normal spirometry, bronchoprovocation with a methacholine challenge test (**Option C**) can be used to identify bronchial hyperresponsiveness. Bronchial challenge testing uses a controlled inhaled stimulus to induce bronchospasm in association with spirometry; a positive test is indicated by a drop in the measured FEV_1. Due to the risk of an exaggerated response as well as difficulties with interpretation, methacholine challenge testing is contraindicated in patients with airflow limitation (FEV<60% of predicted or FEV_1 <1.5 L in adults). In this patient with an FEV_1 of 55% of predicted, methacholine challenge testing would be inappropriate.

KEY POINT

- When an occupational lung disease is suspected, clinicians should request a Safety Data Sheet (SDS) from the patient's employer; the SDS details chemical properties and known health risks associated with substances at the workplace.

Bibliography

Rosenman K, Reilly MJ, Pechter E, et al. Cleaning products and work-related asthma, 10 year update. J Occup Environ Med. 2020;62:130-137. [PMID: 31895737] doi:10.1097/JOM.0000000000001771

Item 26 Answer: D

Educational Objective: **Diagnose diffuse parenchymal lung disease.**

The most appropriate diagnostic test to perform next is high-resolution chest CT (HRCT) (**Option D**). This patient has symptoms and clinical findings suggestive of a diffuse parenchymal lung disease (DPLD). Nonproductive cough and dyspnea are the most common presenting symptoms of DPLD. Findings on chest auscultation can be variable, but the presence of inspiratory dry crackles and clubbing is compatible with a DPLD such as idiopathic pulmonary fibrosis. Other findings supporting the diagnosis of DPLD include chest radiograph showing small lung volumes, unexplained bibasilar infiltrates, restrictive physiology, and a reduced DLCO. HRCT will help confirm the diagnosis of DPLD and may also narrow the differential diagnosis. For example, the addition of expiratory images can help diagnose small airway disease, and prone images can help exclude dependent atelectasis as a potential confounder. In an appropriate clinical setting, typical HRCT findings may obviate the need for lung biopsy.

The findings on HRCT highly correlate with histopathology identified on open lung biopsy; consequently, biopsy is not uniformly required to establish a diagnosis. Lung biopsy, either bronchoscopic (**Option A**) or surgical, may be considered in settings in which pulmonary function tests and HRCT are insufficient to make a diagnosis.

In the evaluation of dyspnea, cardiopulmonary exercise testing (**Option B**) can be helpful if the initial evaluation is unrevealing, deconditioning is a possibility, or multiple problems may be contributing to dyspnea. However, this patient's symptoms, chest radiograph, and spirometry suggest a DPLD. Cardiopulmonary exercise testing will not add to the diagnostic yield.

CT angiography (**Option C**) of the chest will also provide a reasonable assessment of the pulmonary parenchyma and is the diagnostic modality of choice for pulmonary embolism, an unlikely diagnosis for a patient with dyspnea progressing over 7 months. In addition, contrast is not needed for the delineation of DPLDs and adds the unnecessary risk of contrast-induced nephropathy. Although the addition of contrast can help delineate mediastinal lymphadenopathy, there is no suggestion of lymphadenopathy on this patient's chest radiograph.

Evaluation with transthoracic echocardiogram (**Option E**) can be used to exclude left-sided heart failure and assess for pulmonary hypertension. This patient, however, does not have any clinical or radiologic signs of heart failure (elevated central venous pressure, S_3, edema, cardiomegaly, pulmonary congestion) or pulmonary hypertension (fixed splitting of S_2, prominent venous *a* wave, enlarged central pulmonary arteries, and prominent right ventricle).

KEY POINT

- In a patient with a clinical picture suggestive of diffuse parenchymal lung disease, high-resolution CT is the most appropriate diagnostic test.

Bibliography

Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018; 378:1811-1823. [PMID: 29742380] doi:10.1056/NEJMra1705751

Item 27 Answer: C

H

Educational Objective: **Treat pulmonary embolism in a pregnant woman.**

The most appropriate treatment is low-molecular-weight heparin (**Option C**). The American Society of Hematology (ASH) 2018 guidelines for management of venous thromboembolism in the context of pregnancy recommend low-molecular-weight heparin (LMWH). LMWH is strongly recommended over unfractionated heparin (UFH). Antithrombotic therapy markedly reduces mortality in nonpregnant and pregnant patients with acute venous thromboembolism (VTE). LMWH is at least as effective as UFH in the treatment of VTE in pregnant patients, and the risks of bleeding are similar with the two agents. Extended use of UFH during pregnancy is associated with a risk of osteoporotic fracture of 2.2%. There is limited data on bone health in pregnant women receiving LMWH, but in nonpregnant women the risk of fracture appears to be higher in women receiving UFH compared with LMWH. In addition, the risk of heparin-induced thrombocytopenia is higher in nonpregnant women treated with UFH compared with LMWH (2.7% versus 0%). Finally, the ASH guideline notes that the dosing of LMWH is more predictable than UFH, and laboratory testing is generally unnecessary, making treatment more convenient.

There is limited data on the safety of the direct oral anticoagulants (dabigatran, apixaban, edoxaban, and rivaroxaban) (**Options A, D**) in pregnant women. Since they are likely to cross the placenta and their reproductive effects in humans are unknown, the ASH guideline does not recommend them for pregnant women. Finally, dabigatran is not approved as monotherapy for VTE; it must be preceded by heparin therapy.

Fondaparinux (**Option B**) is not recommended for first-line therapy of VTE in pregnancy because this drug has been reported to cross the placenta in small amounts, and experience with fondaparinux in pregnancy is very limited (especially during the first trimester).

Vitamin K antagonists such as warfarin (**Option E**) are not considered acceptable therapy for pregnancy-associated VTE. Warfarin crosses the placenta and has the potential to cause teratogenicity, pregnancy loss, fetal bleeding, and neurodevelopmental deficits. In pregnant patients with VTE, acceptable alternatives are available. Warfarin is recommended in pregnant women with mechanical heart valves if the dose is less than 5 mg daily.

KEY POINTS

- In pregnant patients, low-molecular-weight heparin is the preferred treatment for venous thromboembolism disease.

(Continued)

KEY POINTS *(continued)*

- Because there are limited data on the safety of direct oral anticoagulants and fondaparinux in pregnancy, they are not recommended.

Bibliography

Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2:3317-3359. [PMID: 30482767] doi:10.1182/bloodadvances.2018024802

Item 28 Answer: A

Educational Objective: Diagnose the cause of acute respiratory deterioration in a critically ill patient with bedside thoracic ultrasonography.

The most appropriate next step is to perform bedside ultrasonography (**Option A**). Point-of-care thoracic ultrasonography provides a noninvasive means of rapidly assessing the lungs, pleura, and diaphragm. It is particularly helpful for critically ill patients when the use of imaging techniques requiring transport would delay diagnosis. Thoracic ultrasonography can determine the presence or absence of a pneumothorax or pleural effusion and can characterize the lung parenchyma to aid in the detection of heart failure or pneumonia. Potential causes of worsening gas exchange include increasing pleural effusion, development of a pneumothorax, and worsening of underlying pneumonia or heart failure, all of which can be rapidly assessed using point-of-care ultrasonography.

CT of the chest (**Option B**) is an option, but it will take longer to perform than bedside thoracic ultrasonography, which will delay diagnosis and will also require transport of an unstable patient.

The use of paralytic agents such as cisatracurium (**Option C**) in patients with severe acute respiratory distress disorder (ARDS) may improve oxygenation, decrease ventilator-induced lung injury, and reduce mortality. Indications include agitation, undesired movement, and ventilator dyssynchrony. However, use of these agents is not first-line therapy for these conditions and is typically initiated only when sedation and analgesia fail to control these symptoms. However, this patient has not yet been diagnosed with ARDS, and there is likely another more easily reversible cause for this patient's acute decline that can be diagnosed with bedside thoracic ultrasonography.

Tension pneumothorax should be suspected in patients presenting with significant cardiorespiratory distress (worsening dyspnea, hypotension, absent breath sounds on one side, tracheal deviation, and distended neck veins). A tension pneumothorax that is large and hemodynamically significant should be managed by emergent needle thoracostomy (**Option D**) followed by thoracostomy tube placement and hospitalization. The patient's findings do not fully support the diagnosis of tension pneumothorax, and emergent needle thoracostomy is not indicated. Bedside thoracic ultrasonography may quickly provide a diagnosis and guide appropriate therapy.

KEY POINTS

- Point-of-care thoracic ultrasonography can determine the presence or absence of a pneumothorax or pleural effusion and can characterize the lung parenchyma to aid in the detection of heart failure or pneumonia.
- Point-of-care thoracic ultrasonography is particularly helpful for critically ill patients when the use of imaging techniques requiring transport would delay diagnosis.

Bibliography

Mayo PH, Copetti R, Feller-Kopman D, et al. Thoracic ultrasonography: a narrative review. Intensive Care Med. 2019;45:1200-1211. [PMID: 31418060] doi:10.1007/s00134-019-05725-8

Item 29 Answer: D

Educational Objective: Diagnose small cell lung cancer.

The most likely diagnosis is small cell lung cancer (**Option D**). There are two major classes of lung cancer: non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Small cell lung cancer typically presents as bulky symptomatic masses with mediastinal involvement. It originates from neuroendocrine cell precursors and is characterized by rapid growth and early metastases. Extrathoracic spread is present in 75% to 80% of patients at initial diagnosis. Symptom onset is rapid (typically <8-12 weeks) and includes cough, wheezing, dyspnea, hemoptysis, weight loss, fatigue, anorexia, and manifestations of paraneoplastic syndromes. The most frequent paraneoplastic syndrome is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). This syndrome results from production of antidiuretic hormone by malignant cells. Other paraneoplastic syndromes associated with SCLC include Cushing syndrome, Lambert-Eaton syndrome, encephalomyelitis, and sensory neuropathy. This patient has a lung mass with bulky mediastinal lymphadenopathy and hyponatremia (secondary to SIADH), making small cell lung cancer the most likely diagnosis.

Approximately 80% of lung cancer cases are NSCLC, which is divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma (**Option A**) is the most common NSCLC and accounts for almost all lung cancer diagnoses in nonsmokers. The most frequent location of adenocarcinoma is in the peripheral aspects of the lung parenchyma as a solitary nodule or mass. Squamous cell carcinoma is the second most common subtype of NSCLC. It correlates highly with smoking history and usually originates in the central airways. Large cell carcinoma (**Option C**) is an undifferentiated carcinoma and characteristically presents as a peripheral mass with prominent necrosis. Adenocarcinoma and large cell carcinoma are not associated with SIADH-related hyponatremia.

Fibrosing mediastinitis (**Option B**) is a rare complication of previous histoplasmosis. It is characterized by an excessive fibrotic reaction in the mediastinum and can cause compression of adjacent structures, such as the airways, vessels, and

H CONT.

esophagus. Fibrosing mediastinitis usually affects younger patients, slowly progresses over 2 to 5 years, and has calcifications on imaging. Thus, it is an unlikely diagnosis in this patient.

KEY POINT

- Small cell lung cancer typically presents as bulky symptomatic masses with mediastinal involvement, and is associated with paraneoplastic syndromes—most frequently, the syndrome of inappropriate antidiuretic hormone secretion.

Bibliography

Wang S, Zimmermann S, Parikh K, et al. Current diagnosis and management of small-cell lung cancer. Mayo Clin Proc. 2019;94:1599-1622. [PMID: 31378235] doi:10.1016/j.mayocp.2019.01.034

Item 30 Answer: B

Educational Objective: **Treat idiopathic pulmonary fibrosis.**

The most appropriate treatment is antifibrotic therapy with pirfenidone (**Option B**). This patient has idiopathic pulmonary fibrosis (IPF). Patients with IPF present with chronic shortness of breath and a dry cough. Patients typically have bibasilar inspiratory Velcro-like crackles, and clubbing is common. The prevalence of disease increases with age. A confident diagnosis can be made based on the presence of typical symptoms and a usual interstitial pneumonia pattern on a high-resolution CT scan of the chest. IPF is progressive, with a median survival of 3 to 5 years after diagnosis. In 2014 the FDA approved two medications: pirfenidone, an antifibrotic agent, and nintedanib, a tyrosine kinase inhibitor, for use in patients with IPF. In clinical trials the two agents were found to have comparable efficacy in mitigating the rate of FVC decline by approximately 50% over the course of 1 year. They have also shown some efficacy in reducing severe respiratory events such as acute exacerbations and hospitalization. Common side effects are anorexia, nausea, photosensitivity (pirfenidone), and diarrhea (nintedanib). Although these medications delay IPF progression, they are not curative. Referral to a pulmonologist or interstitial lung disease center may be appropriate before initiating treatment with these medications. Lung transplantation is a life-prolonging therapy for those without comorbidities that may otherwise limit life expectancy. Early referral of eligible patients to a transplant center is appropriate given the unpredictability of disease progression.

A clinical trial of *N*-acetylcysteine monotherapy (**Option A**) did not show any benefit in patients with IPF. Interferon-γ and endothelin antagonists have also been found to be ineffective.

A combination regimen of prednisone with azathioprine and *N*-acetylcysteine (**Option C**) is associated with an increase in mortality in IPF. Hence, treatment guidelines for IPF make a strong recommendation against its use.

Treatment with warfarin (**Option D**) has also not shown any benefit and is associated with an increased risk of mortality in patients who lack other indications for anticoagulation.

KEY POINTS

- Therapy with pirfenidone or nintedanib decreases the rate of progression of idiopathic pulmonary fibrosis but is not curative.
- In patients with idiopathic pulmonary fibrosis, lung transplantation is a life-prolonging therapy for those without comorbidities that may otherwise limit life expectancy.

Bibliography

Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018; 378:1811-1823. [PMID: 29742380] doi:10.1056/NEJMra1705751

Item 31 Answer: D

H

Educational Objective: **Minimize sedation in ventilated patients in the ICU.**

The most appropriate management is to hold the sedation and analgesia infusions (**Option D**). For acutely hospitalized patients ventilated for more than 24 hours, guidelines suggest protocols to reduce sedation. Sedative-analgesic medications can cause excess sedation and may prolong the duration of mechanical ventilation. In randomized clinical trials, two strategies have been shown to be effective in reducing the duration of mechanical ventilation and its associated complication. The first strategy consists of intermittent intravenous administration of analgesia without sedatives (analgesia first approach). A second strategy consists of daily interruption of continuous infusion of analgesics and sedatives. Variations of these protocols exist, including targeting light sedation. The optimal strategy is not known, and guidelines offer no preference due to insufficient data, but all have in common periods of time in which the patient is awake. When implemented routinely, protocols that limit sedation or allow spontaneous awakening will decrease the length of mechanical ventilation, ICU stay, and incidence of delirium. In this deeply sedated patient, stopping sedation and analgesics now will allow the fastest decrease in medication levels, thus allowing assessment of the patient.

Titration of sedation medication (**Option A**) will also lead to arousal. However, the time to reach steady state after decreasing the infusion rate of a sedative is prolonged (7 half-lives), thus prolonging the time until an appropriate neurologic examination.

Electroencephalography (**Option B**) remains a key diagnostic tool for critically ill patients with unexplained altered mental status because the incidence of nonconvulsive seizures has been reported to be as high as 43% in critically ill patients with encephalopathy. But the first step should be to stop the medication effects before initiating other diagnostic evaluations.

H CONT.

A head CT (**Option C**) is unlikely to yield any relevant information in this patient. A neurologic examination, for which sedation should be held, should guide the decision to perform any imaging studies.

KEY POINTS

- Sedative-analgesic medications can cause excess sedation and may prolong the duration of mechanical ventilation.
- For acutely hospitalized patients ventilated for more than 24 hours, guidelines suggest protocols to reduce sedation.

Bibliography

Ervin JN, Rentes VC, Dibble ER, et al. Evidence-based practices for acute respiratory failure and acute respiratory distress syndrome: A systematic review of reviews. Chest. 2020;158:2381-2393. [PMID: 32682771] doi:10.1016/j.chest.2020.06.080

H

Item 32 Answer: B

Educational Objective: **Diagnose a chylothorax.**

The most likely diagnosis is chylothorax (**Option B**). Chylothorax refers to the presence of chyle within the pleural space. Chylothorax has both traumatic and nontraumatic causes. The most common traumatic cause is thoracic surgery. Esophagostomy carries the highest risk followed by mediastinal lymph node dissection, mediastinal tumor resection, and any surgery involving the lower neck and mediastinum. The most common nontraumatic cause is malignancy, of which lymphoma is the most common. Other possible nontraumatic causes include lymphatic disorders and chylous ascites. In patients with nontraumatic cases, the mechanism of the chylothorax varies with the underlying cause. In this patient it is most likely secondary to compressive obstruction due to bulky lymphadenopathy. Chest pain and fever are rare in patients with chylothorax, but the presence of fever may represent an underlying lymphoma. Chylous effusions have a high protein concentration making them exudates by Light's criteria. The explanation for elevated protein in a chylous effusion is unknown. The pleural fluid lactate dehydrogenase (LDH) is typically low, reflective of a transudate. If elevated, it often reflects the underlying cause of the effusion, such as a malignancy. A chylothorax is diagnosed by a triglyceride level greater than 110 mg/dL (1.24 mmol/L), and it is typically a lymphocytic predominant effusion. Although chylothorax is often milky in appearance, as is a cholesterol effusion, it can appear serous or sanguineous.

A cholesterol effusion (**Option A**) is diagnosed by a pleural fluid cholesterol level greater than 200 mg/dL (5.18 mmol/L). Cholesterol effusions are quite rare and when present are most commonly associated with tuberculosis, rheumatoid effusions, and other chronic pleural effusions.

Empyema (**Option C**) is incorrect as the patient has no clinical features of infection (fever, chest pain, leukocytosis). In addition, empyema is not milky in appearance and is typically associated with a low pleural fluid pH and low glucose.

A rheumatoid effusion (**Option D**) is typically an inflammatory effusion with a low pH (<7.2), a low glucose level (<40 mg/dL [2.2 mmol/L]), and an elevated LDH level.

KEY POINTS

- A chylothorax is diagnosed by a triglyceride level greater than 110 mg/dL (1.24 mmol/L), and it is typically a lymphocytic predominant exudative effusion.
- The most common nontraumatic cause of chylothorax is malignancy, of which lymphoma is the most common.

Bibliography

Feller-Kopman D, Light R. Pleural disease. N Engl J Med. 2018;378:740-751. [PMID: 29466146] doi:10.1056/NEJMra1403503

Item 33 Answer: B

Educational Objective: **Diagnose idiopathic pulmonary fibrosis.**

The most likely diagnosis is idiopathic pulmonary fibrosis (IPF) (**Option B**). IPF is associated with the histopathologic appearance of usual interstitial pneumonia, the most common idiopathic form of diffuse parenchymal lung disease (DPLD). It typically presents in patients between 50 and 70 years of age who have a greater than 6-month duration of a dry cough and dyspnea on exertion. History will reveal no potential cause for the development of fibrosis, and lung examination is notable for Velcro-like inspiratory crackles that are predominant at the bases. Clubbing is present in up to 50% of patients. The best diagnostic test is high-resolution CT (HRCT) of the chest, which may show abnormalities such as bilateral, peripheral, and basal predominant septal line thickening with honeycomb changes. The most appropriate next step in this patient's management is to discuss the patient's diagnosis in a multidisciplinary meeting involving a thoracic radiologist, a pathologist, and a pulmonologist; a multidisciplinary discussion may yield a confident diagnosis of IPF, without the need for a lung biopsy.

Patients with cryptogenic organizing pneumonia (COP) (**Option A**) typically present with cough, fever, and malaise for 6 to 8 weeks. Initial chest radiographs will demonstrate patchy opacities that mimic pneumonia, and as a result, patients are often initially misdiagnosed with community-acquired pneumonia and treated with standard antibiotics. HRCT scans will demonstrate ground-glass opacities or areas of alveolar consolidation resembling an infectious pneumonia, but findings can include peripheral nodules and nodules along the bronchovascular bundle. This patient's age, long duration of symptoms, and honeycomb changes on HRCT scan do not fit the clinical picture of COP.

Nonspecific interstitial pneumonia (NSIP) (**Option C**) is the most common DPLD associated with autoimmune disorders, but it can occasionally be idiopathic. NSIP affects a younger population than IPF. HRCT scans will demonstrate bilateral lower-lobe reticular changes and an absence of honeycombing, but they can also demonstrate areas of ground-glass opacification. In this patient, the lack of an underlying autoimmune disease, older age, and HRCT findings are not consistent with NSIP.

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) (**Option D**) is the histopathologic diagnosis associated with the HRCT finding of centrilobular micronodular disease in current smokers. On physiologic testing, RB-ILD may have combined restriction and obstruction. The patient is not an active smoker, which argues against RB-ILD.

KEY POINT

- Idiopathic pulmonary fibrosis presents in patients between 50 and 70 years of age, greater than 6 months' duration of a dry cough and dyspnea on exertion, Velcro-like crackles, clubbing (50%), and honeycomb changes on HRCT scans.

Bibliography

Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378:1811-1823. [PMID: 29742380] doi:10.1056/NEJMra1705751

Item 34 Answer: C

Educational Objective: **Treat high-altitude pulmonary edema.**

The most appropriate additional treatment is descent to a lower altitude (**Option C**) as soon as possible. The patient is experiencing high-altitude pulmonary edema (HAPE), which is caused by exaggerated hypoxic pulmonary vasoconstriction and abnormally high pulmonary artery and capillary pressures. The resulting leakage of edema fluid into the alveolus causes hypoxemia and may evoke an inflammatory response. Risks for this disorder include rapid ascent to altitudes greater than 2500 meters (~8200 feet), the actual altitude attained, time spent at altitude, and a history of high-altitude illness. The typical symptoms of HAPE (cough, shortness of breath, and fatigue) can be difficult to distinguish from pneumonia. As HAPE progresses, patients can develop pink frothy sputum, hemoptysis, and life-threatening hypoxemia. Treatment of HAPE focuses on promptly reducing the pulmonary artery pressure. This can be done by providing supplemental oxygen, limiting the patient's physical exertion and cold exposure, and advising the patient to descend to a lower altitude as soon as possible. This patient has received supplemental oxygen and should descend to a lower altitude. Some clinicians suggest the use of nifedipine as adjunctive therapy, but there is a paucity of data to confirm its benefit.

Acetazolamide (**Option A**) is commonly used for prophylaxis against HAPE, but it has no role in treatment.

Ceftriaxone (**Option B**) would be appropriate if the patient had a concurrent pneumonia along with HAPE. However, given the symptoms and timing of onset in this otherwise healthy patient, there is nothing to suggest a concurrent pneumonia or the need for antibiotics.

Dexamethasone (**Option D**) has been shown to have a role in prophylaxis for high-altitude–related illnesses and as treatment for high-altitude cerebral edema but not for HAPE.

Furosemide (**Option E**) is a loop diuretic that is commonly used in pulmonary edema secondary to heart failure. However, the typical patient with HAPE is not volume overloaded. The use of diuretics in these patients has no role in HAPE and may cause harm by depleting intravascular volume and further reducing oxygen delivery to hypoxic tissues.

KEY POINT

- Treatment of high-altitude pulmonary edema focuses on promptly reducing the pulmonary artery pressure; the patient should be given supplemental oxygen and advised to descend to a lower altitude as soon as possible and to limit physical exertion and cold exposure.

Bibliography

Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. Eur Respir Rev. 2017;26. [PMID: 28143879] doi:10.1183/16000617.0096-2016

Item 35 Answer: D

Educational Objective: **Treat sepsis with a balanced crystalloid solution.**

The most appropriate resuscitative treatment for this patient is lactated Ringer solution (**Option D**). The patient most likely has sepsis or septic shock based on a source of infection, fever, hypotension, tachycardia, and altered mentation. Sepsis and septic shock are medical emergencies, and treatment with fluid resuscitation begins immediately. Guidelines recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid be given within the first 3 hours with either balanced crystalloid solution such as lactated Ringer solution or 0.9% saline. However, a large 2018 clinical trial demonstrated that among critically ill adults, the use of a balanced crystalloid solution for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal replacement therapy, or persistent renal dysfunction than the use of 0.9% saline, with an absolute difference of 1.1%.

Three large trials have evaluated the benefits of albumin administration (**Option A**) compared with crystalloid solutions. Although prespecified subgroup analyses in two of the trials initially suggested that albumin may improve survival over crystalloids in patients with septic shock, more recent meta-analyses suggest otherwise. Because albumin is significantly more expensive than crystalloid solutions, it is not recommended for routine use in resuscitation of patients with septic shock.

Bicarbonate solutions (**Option B**) are not recommended as a standard part of sepsis or septic shock resuscitation and would not benefit this patient. Even in patients with an increased anion gap acidosis, administration of bicarbonate

H CONT.

solution is not associated with improved outcomes and can have adverse effects such as hypocalcemia, hypercapnia, and QT prolongation.

Guidelines recommend against using hydroxyethyl starches (HESs) (**Option C**) for intravascular volume replacement in patients with sepsis or septic shock due to a lack of data showing superiority to crystalloid solutions and safety concerns. A network meta-analysis focused on acute resuscitation of patients with sepsis or septic shock found that HESs resulted in a higher risk of death and need for renal replacement therapy compared with crystalloids.

KEY POINTS

- Sepsis and septic shock are medical emergencies, and fluid resuscitation should begin immediately.
- Guidelines recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of intravenous crystalloid fluid be given within the first 3 hours.

Bibliography

Semler MW, Self WH, Wanderer JP, et al; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378:829-839. [PMID: 29485925] doi:10.1056/NEJMoa1711584

Item 36 Answer: A

Educational Objective: **Evaluate an 8-mm ground-glass (subsolid) pulmonary nodule with serial CT scans.**

The most appropriate management is chest CT every 2 years for 5 years (**Option A**). The patient has an indeterminate pulmonary nodule and requires further follow-up evaluation. Pulmonary nodules can be classified as solid or subsolid. The subsolid nodule classification is further subdivided into pure ground-glass nodules and part-solid nodules. The evaluation of pure ground-glass nodules is informed primarily by nodule size. An incidentally found ground-glass nodule of 6 mm or larger necessitates follow-up chest CT at 6 to 12 months. If the nodule persists but is unchanged in size, as in this patient, chest CT should be repeated at 2-year intervals for 5 years. Earlier follow-up is unlikely to affect the outcome of these characteristically indolent lesions. Studies have shown that an average of 3 to 4 years is typically required to establish growth or, less commonly, to diagnose a developing invasive carcinoma. Many ground-glass nodules resolve spontaneously because they can also be from infectious or inflammatory causes. If the nodule resolves, no further follow-up is needed. If the nodule grows or develops a solid component, biopsy or resection is recommended.

Ground-glass nodules are associated with more indolent histologic lesions (e.g., adenocarcinoma in situ and minimally invasive adenocarcinoma), which require longer follow-up to determine whether they are benign. Thus, it is not appropriate to perform follow-up CT at 12 months (**Option B**) with no further testing if the scan is normal.

The indolence of ground-glass nodules and their very low metabolic activity also makes fluorodeoxyglucose PET less useful (**Option C**); PET scans in this setting can show false-positive results.

Resection (**Option D**) would not be recommended at this point because it would subject the patient to a surgery that may be unnecessary given the indeterminate nature of the nodule.

KEY POINT

- An incidentally found ground-glass (subsolid) pulmonary nodule 6 mm or larger necessitates follow-up chest CT at 6 to 12 months; if it persists but is unchanged in size, CT should be repeated at 2-year intervals for 5 years.

Bibliography

MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

Item 37 Answer: B

Educational Objective: **Evaluate suspected pulmonary hypertension.**

The most appropriate diagnostic test to perform is echocardiography (**Option B**). Approximately 10% of patients with systemic sclerosis develop pulmonary arterial hypertension (PAH), a significant cause of morbidity and mortality. Symptoms of pulmonary hypertension (PH) are nonspecific; thus, the average time from symptom onset to diagnosis can exceed 2 years. Symptoms include exertional dyspnea or lightheadedness, lower extremity edema, chest pain, palpitations, and in some cases, syncope. Findings on physical examination frequently include an accentuated or persistently split S_2. A holosystolic tricuspid regurgitant murmur, jugular venous distention, a right ventricular heave, hepatomegaly, ascites, and peripheral edema occur in the face of progressive right ventricular failure. Pulmonary findings reflect underlying lung disease when present. If PAH is suspected, transthoracic echocardiography should be pursued. Echocardiography provides an estimation of mean pulmonary artery systolic pressure and assessment of both right and left heart size and function. If the echocardiogram suggests PH, the patient should be referred for further evaluation, including right heart catheterization. In patients with systemic sclerosis, guidelines suggest annual screening with echocardiography for PH.

CT angiography (**Option A**) can be used to evaluate for the presence of acute pulmonary embolism. Since the patient's symptoms are progressive over months, the likelihood of acute pulmonary embolism is very low. CT angiography is not the best initial diagnostic test for this patient.

Patients with systemic sclerosis are at increased risk for developing coronary artery disease and interstitial lung disease. In a patient with progressive dyspnea, both diseases should be considered. However, this patient's findings of increased jugular venous distention, persistently split S_2, and tricuspid regurgitant murmur suggest PAH. The patient's pulmonary examination and chest radiograph are normal. An exercise stress test (**Option C**) or pulmonary function testing (**Option D**) may be indicated if the patient's echocardiogram is unremarkable, but neither is the best initial choice in light of her physical examination findings.

KEY POINTS

- Physical examination findings of pulmonary hypertension may include accentuated or persistently split S_2, holosystolic tricuspid regurgitant murmur, jugular venous distention, right ventricular heave, hepatomegaly, ascites, and peripheral edema.
- Transthoracic echocardiography is indicated in patients with suspected pulmonary hypertension.

Bibliography

Jiang Y, Turk MA, Pope JE. Factors associated with pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc). Autoimmun Rev. 2020; 19:102602. [PMID: 32659476] doi:10.1016/j.autrev.2020.102602

Item 38 Answer: A

Educational Objective: Assess adherence to positive airway pressure therapy.

The most appropriate management is to assess the patient's adherence to positive airway pressure (PAP) therapy (**Option A**). This patient has severe, symptomatic obstructive sleep apnea (OSA), for which PAP is preferred therapy. The response to treatment depends on adherence; a substantial proportion of patients, particularly early in the course of therapy, do not use PAP as intended (all night, every night). Symptom burden probably drives adherence, but for those who lack motivation, educational programs can help, as can direct-to-patient reports wirelessly transmitted from the device to smartphones or computers. Adherence might be improved by addressing common adverse effects. Side effects such as xerostomia and nasal dryness and congestion can be ameliorated by in-line humidification. Intranasal glucocorticoids or anticholinergics may be useful for recalcitrant nasal congestion or rhinitis. Modified pressure profiles that slightly reduce pressure on exhalation may enhance comfort. Proper mask fit enhances comfort and mitigates air leak. PAP interfaces, ranging from nasal pillows that sit at the nasal openings to nasal masks that cover the nose to oronasal (full face) masks that cover the nose and mouth, are frequently updated and improved and may improve adherence. Download of data from the PAP device yields important information about use that the physician can discuss with the patient to explore barriers and formulate a plan to promote adherence.

Bilevel positive airway pressure (**Option B**) is considered preferred therapy in hypoventilation syndromes such as those associated with neuromuscular disease or severe COPD, but little evidence supports its superiority in promoting treatment adherence for OSA.

Two small randomized controlled trials showed that eszopiclone (**Option C**) administered early in the course of continuous positive airway pressure (CPAP) led to modest improvements in CPAP adherence. However, the role of such hypnotic agents in promoting CPAP adherence remains controversial. Their use later in the course of PAP, as in this patient, is unknown, and the risk for adverse effects may outweigh their benefit.

Modafinil (**Option D**) is a stimulant medication that can be used for residual excessive sleepiness in patients with OSA who are using PAP optimally. The patient's adherence to PAP therapy is not yet known, so it is not appropriate to prescribe modafinil.

KEY POINTS

- The treatment response for patients with sleep apnea depends on adherence to positive airway pressure therapy and should be assessed in all patients.
- Download of adherence data from the positive airway pressure device yields important information about use that can be discussed with the patient with sleep apnea to explore barriers and formulate a plan to promote adherence.

Bibliography

Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2019;15:335-343. [PMID: 30736887] doi:10.5664/jcsm.7640

Item 39 Answer: B

Educational Objective: Diagnose a complicated parapneumonic effusion.

The diagnostic test that will be most helpful in directing therapy is pleural fluid pH (**Option B**). The patient presents with severe community-acquired pneumonia and an associated pleural effusion (parapneumonic effusion). A parapneumonic effusion can be either uncomplicated (sterile and free flowing) or complicated (infected or loculated). An uncomplicated effusion is typically small and can resolve on its own. A complicated parapneumonic effusion occurs when there has been bacterial invasion across the pleural mesothelium, stimulating a significant inflammatory response. A diagnostic thoracentesis should be performed to assess the pleural effusion. A parapneumonic effusion is considered complicated when an exudative effusion has either or both of the following characteristics: pH less than 7.2 (or glucose <40 mg/dL [2.2 mmol/L] in the absence of pH data) or evidence of microorganism invasion by culture or Gram stain. In the setting of suspected infection, a pleural fluid pH level of less than 7.2 is the best indicator of a complicated pleural effusion that requires drainage. Ultrasonography also has been found useful in the determination of a complicated parapneumonic effusion and has a sensitivity of 69% and specificity of 90% when complexity is seen.

CONT.

A pleural-fluid lactate dehydrogenase (LDH) (**Option A**) level greater than two thirds of the upper limit of normal for serum LDH may support the diagnosis of an exudate in this patient, but it is nonspecific and may simply be an indicator of inflammation rather than infection of the pleural space.

Pleural fluid procalcitonin measurement (**Option C**) has been studied as a method to differentiate parapneumonic and tuberculous pleural effusions from other causes of exudative effusions and to differentiate parapneumonic from tuberculous pleural effusions. However, studies have failed to demonstrate the value of procalcitonin measurement, and it is not recommended.

Total protein measurements (**Option D**) are helpful in characterizing the pleural fluid as exudative by Light's criteria (ratio of pleural-fluid protein to serum protein level >0.5). However, total pleural fluid protein measurements do not differentiate between a complicated and an uncomplicated parapneumonic effusion.

KEY POINT

- In the setting of suspected infection, a pleural fluid pH level of less than 7.2 (or glucose <40 mg/dL [2.2 mmol/L] in the absence of pH data) is the best indicator of a complicated pleural effusion that requires drainage.

Bibliography

Feller-Kopman D, Light R. Pleural disease. N Engl J Med. 2018;378:740-751. [PMID: 29466146] doi:10.1056/NEJMra1403503

Item 40 Answer: C

Educational Objective: **Manage exercise-induced bronchoconstriction.**

The most appropriate management is to begin budesonide-formoterol 5 to 20 minutes before exercise (**Option C**). Exercise-induced bronchoconstriction (EIB) is acute, measurable airway obstruction that occurs in response to exercise. It is one of the most common triggers of symptoms in patients with known asthma. It also occurs in patients without asthma (typically, elite athletes) during periods of high-intensity exercise. Environmental factors such as cold, dry air, exposure to high levels of trichloramines in swimming pools, and inhalation of airborne particulates and ozone can play a key role in precipitating symptoms. For safety, current Global Initiative for Asthma (GINA) guidelines no longer recommend treatment of intermittent asthma, including EIB, with a short-acting β_2-agonist (SABA) alone. All adults should receive a glucocorticoid-containing controller treatment to reduce their risk of serious exacerbations and to control symptoms. The glucocorticoid controller medication can be administered either as regular daily treatment or, in milder asthma, as the combination glucocorticoid-formoterol taken whenever needed for asthma relief. Accordingly, GINA guidelines recommend a daily inhaled glucocorticoid plus a SABA before exercise or low-dose budesonide-formoterol before exercise. Nonpharmacologic measures, including pre-exercise warm-up and warming cold air before inhalation (e.g., with a mask or scarf), are also recommended. In contrast, the 2020 Asthma Guideline Update from the National Asthma Education and Prevention Program has continued the previous recommendation of as-needed SABA-only use for this group of patients.

Use of single-agent LABAs such as salmeterol (**Option A**) is not recommended because of a demonstrated increased risk of asthma-related death when used without a simultaneous controller medication. Clinical trial results show that LABAs used with inhaled glucocorticoids do not significantly increase the risk of asthma-related hospitalization, intubation, or death compared with inhaled glucocorticoids alone, and they result in significantly fewer asthma exacerbations.

Daily use of low-dose inhaled glucocorticoids (**Option B**) would expose this patient to a significantly higher total dose of inhaled glucocorticoids compared with as-needed use. In addition, if daily inhaled controller medication with a glucocorticoid is prescribed, it should usually be accompanied by a SABA before exercise and as needed for quick relief.

In patients with asthma, inhaled ipratropium (**Option D**) is generally not used for quick relief because of its delayed onset and peak action of 15 minutes and 1 to 2 hours, respectively. A SABA is preferred to ipratropium, either with a daily inhaled glucocorticoid or administered with an inhaled glucocorticoid.

KEY POINTS

- Exercise-induced bronchoconstriction is an acute, measurable airway obstruction that occurs in response to exercise.
- Global Initiative for Asthma guidelines recommend that initial pharmacologic therapy for exercise-induced bronchoconstriction should consist of a daily inhaled glucocorticoid plus a short-acting β_2-agonist or low-dose budesonide-formoterol before exercise, whereas the National Asthma Education and Prevention Program recommends a short-acting β_2-agonist.

Bibliography

Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: ginasthma.org/wp-content/uploads/2021/04/GINA-2021-Main-Report_FINAL_21_04_28-WMS.pdf. Accessed May 5, 2021.

Item 41 Answer: B

Educational Objective: **Treat anaphylaxis.**

The most appropriate treatment is epinephrine (**Option B**). This patient has anaphylaxis from a Hymenoptera sting. Anaphylaxis is a severe reaction caused by acute mediator release into the circulation, usually triggered by IgE-linked immunologic responses to specific foods, medications, insect venom, latex, or other antigens but sometimes occurring without an allergic trigger. The mediator release results in various clinical manifestations, including pruritus, hypotension, tachycardia, and airway compromise with bronchoconstriction. Initial treatment of anaphylaxis is with epinephrine, which may be administered intramuscularly or intravenously. Mechanisms of action of epinephrine include vasoconstriction, respiratory smooth muscle relaxation, and stabilization of degranulating inflammatory cells. Some patients, such as this one, require repeat doses of epinephrine or even an intravenous epinephrine infusion if anaphylaxis persists. Patients should be given supplemental oxygen and watched closely for signs of airway compromise, such as stridor or obstruction due to a swollen tongue, which may require intubation to maintain airway patency. Patients often require fluid resuscitation, with or without vasopressor therapy. Factors that increase risk for biphasic anaphylaxis (anaphylaxis occurring 1-72 hours after resolution of the initial episode) include a severe initial episode and a need for more than one dose of epinephrine. When such risk exists, or when there is risk of anaphylaxis fatality due to coexisting cardiovascular disease or lack of access to epinephrine or emergency services, extended observation of up to 6 hours or longer may be warranted.

Antihistamines that antagonize the H$_1$ receptor, such as diphenhydramine (**Option A**), and the H$_2$ receptor, such as famotidine (**Option C**), are often given in the setting of anaphylaxis. However, they are of little proven benefit beyond relief of pruritus and skin eruptions such as urticaria. They do not affect respiratory smooth muscle or vascular tone.

Glucocorticoids such as methylprednisolone (**Option D**) are often given for anaphylaxis, but their efficacy in this setting is not well proved. Furthermore, their delayed onset of action renders them ineffective in the management of early and acute signs and symptoms.

Other vasopressors, such as norepinephrine (**Option E**), might be useful for persistent hypotension and shock but do not correct impairment of other organ systems, such as the respiratory system. Repeat dosing of epinephrine, rather than administration of norepinephrine, is the appropriate intervention for this patient.

KEY POINTS

- Epinephrine is the treatment of choice for anaphylaxis.
- If anaphylaxis persists after an initial epinephrine dose, repeat doses may be needed.

Bibliography

Shaker MS, Wallace DV, Golden DBK, et al; Collaborators. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145:1082-1123. [PMID: 32001253] doi:10.1016/j.jaci.2020.01.017

Item 42 Answer: A

Educational Objective: **Treat unprotected airway with endotracheal intubation.**

The most appropriate treatment is endotracheal intubation (**Option A**). This patient has a toxic syndrome manifesting as respiratory depression, and there is concern for possible aspiration. The circumstances of the toxic syndrome in this patient are unclear and may involve more than one substance. However, a primary consideration is opioid toxicity, with a background of access to methadone, respiratory depression, miotic pupils, depressed level of consciousness, and a transient response of the respiratory rate to naloxone. In addition to identifying the agents or classes of drugs taken, care of patients who have taken an overdose is primarily supportive; maintenance of airway patency and ventilation is critically important in patients with decreased mental status. This patient's inability to protect the airway and concern for aspiration necessitate airway intubation.

Flumazenil (**Option B**), an antagonist of the benzodiazepine receptor, is generally not indicated in patients with depressed consciousness due to polysubstance intoxication because it can precipitate withdrawal seizures. Furthermore, because the respiratory depressant effects of benzodiazepines are proportionally small relative to those of opioids, reversal with flumazenil will not benefit a patient with impending respiratory failure.

Naloxone (**Option C**) is an opioid antidote that can be administered intravenously, intramuscularly, intranasally, and endotracheally. If respiratory depression measurably improves, naloxone can be given in repeated doses or as an intravenous infusion until the opioid is sufficiently metabolized and cleared. In many instances, naloxone can avert the need for mechanical ventilation. In this patient, however, intubation is necessary because of his apparent inability to protect the airway.

Providing higher levels of supplemental oxygen (**Option D**) could modestly raise the patient's blood oxygen levels but will not affect the primary underlying problems of alveolar hypoventilation and inability to protect the airway from aspiration.

KEY POINTS

- Opioid overdose should be suspected in patients with respiratory depression, miotic pupils, and depressed level of consciousness.
- In addition to seeking to identify the specific agents or classes of drugs taken, care of overdose patients is primarily supportive; maintenance of airway patency and ventilation is critically important in patients with decreased mental status.

Bibliography

Skolnik A, Monas J. The crashing toxicology patient. Emerg Med Clin North Am. 2020;38:841-856. [PMID: 32981621] doi:10.1016/j.emc.2020.06.014

Item 43 Answer: D

Educational Objective: **Diagnose occupational asthma.**

The most likely diagnosis is occupational asthma (**Option D**). This patient presents with one of the most common types of occupational asthma, bakers' asthma. Occupational asthma includes both asthma caused by exposure to sensitizing or irritant substances in the workplace and preexisting asthma that is exacerbated by these same factors. Typical sensitizing agents are high-molecular-weight substances, such as proteins, that induce an IgE-mediated immunologic response. In bakers' asthma, exposure to proteins in wheat and rye flour is a likely cause. Once sensitized, patients may react to very low levels of exposure. A key clinical indicator is the relationship of symptoms to work exposure; patients often improve on weekends and during time away from work. Spirometry before and after workplace exposures is a cost-effective way to confirm a suspected diagnosis of occupational asthma. Alternatively, serial peak flow measurements can be used. In addition to pharmacologic therapy, treatment consists of reducing exposure to the offending agent through workplace modifications or removing patients from the workplace entirely.

Acute bronchitis (**Option A**) is a lower respiratory tract infection of the large airways, often caused by viral pathogens. It is often preceded by symptoms of upper respiratory tract infection such as headache, sore throat, and rhinitis. Most cases of acute bronchitis are self-limiting and resolve within 1 to 3 weeks. Although this patient's symptoms are similar to those of bronchitis, the symptom duration and improvement away from the workplace suggest a different cause.

Acute hypersensitivity pneumonitis (**Option B**) is also caused by inhalation of sensitizing antigens, but it leads to a markedly different clinical syndrome than occupational asthma. It is characterized by fever, cough, and fatigue within 12 hours of a major exposure to an inciting antigen. Inspiratory crackles are heard during physical examination.

Allergic bronchopulmonary aspergillosis (ABPA) (**Option C**) is an ongoing immunologic response to inhaled *Aspergillus*. The reaction leads to persistent eosinophilic airway inflammation, increased IgE levels, and eventually tissue damage with airway remodeling. Diagnostic criteria include the presence of asthma, elevated IgE levels, positive skin tests to *Aspergillus* antigens, increased pulmonary *Aspergillus*-specific IgE and IgG levels, and either central bronchiectasis or infiltrates. The patient's normal *Aspergillus*-specific IgE level and chest radiograph do not support a diagnosis of ABPA.

KEY POINTS

- Occupational asthma includes asthma caused by exposure to sensitizing or irritant substances in the workplace, including high-molecular-weight substances, such as proteins, that induce an IgE-mediated immunologic response.
- Occupational asthma is characterized by an improvement in symptoms when the patient is away from work.

Bibliography

Cormier M, Lemière C. Occupational asthma. Int J Tuberc Lung Dis. 2020; 24:8-21. [PMID: 32005302] doi:10.5588/ijtld.19.0301

Item 44 Answer: B

Educational Objective: **Treat COPD with lung volume reduction surgery.**

The most appropriate therapy for this patient is lung volume reduction surgery (**Option B**). Lung volume reduction surgery improves quality of life, exercise tolerance, pulmonary function, and survival in patients with emphysema. The National Emphysema Treatment Trial also found that success relied on ideal patient selection. Ideal patients are those with upper-lobe-predominant emphysema, FEV_1 and DLCO of 20% of predicted or higher, and low exercise tolerance after completion of pulmonary rehabilitation. Patients with an FEV_1 of less than 20% of predicted, a DLCO of less than 20% of predicted, or non-upper-lobe-predominant disease had high mortality rates. Bronchoscopic surgery is also a possible therapeutic option. Carefully selected patients who received endobronchial valve therapy have a greater likelihood of an increase in their FEV_1 of 15% or greater, significant improvements in their 6-minute walk distances, and improvements in their dyspnea.

Macrolide antibiotics such as azithromycin (**Option A**) have anti-inflammatory and antimicrobial effects. Long-term macrolide therapy may reduce the frequency of exacerbations when prescribed to patients with severe COPD and a history of frequent exacerbations. Chronic antibiotic therapy is not indicated for most patients with COPD, and this patient has no indication for chronic antibiotic therapy.

Roflumilast (**Option C**) is a selective phosphodiesterase-4 inhibitor that is used to reduce chronic symptoms and the frequency of exacerbations in patients with severe COPD who have either primarily symptoms of chronic bronchitis or frequent exacerbations. This patient with symptoms and radiographic findings most consistent with emphysema and no history of frequent exacerbations does not have an indication for roflumilast therapy.

The patient had a minimum oxygen saturation of 90% during a 6-minute walk test. Supplemental oxygen therapy (**Option D**) improves quality of life and decreases mortality for patients with COPD and an arterial PO_2 of 55 mm Hg (7.3 kPa) or less or an oxygen saturation of 88% or less. For patients with COPD and comorbidities such as erythrocytosis, heart failure, or cor pulmonale, supplemental oxygen is reasonable if the arterial PO_2 is 59 mm Hg (7.8 kPa) or less or oxygen saturation is 89% or less. This patient does not meet the criteria for supplemental oxygen.

KEY POINTS

- Lung volume reduction surgery improves quality of life, exercise tolerance, pulmonary function, and survival in selected patients with emphysema.
- Ideal patients for lung volume reduction therapy are those with upper-lobe-predominant emphysema, FEV_1 and DLCO of 20% of predicted or higher, and low exercise tolerance after completion of pulmonary rehabilitation.

Bibliography

Global Initiative for Chronic Obstructive Lung Disease. 2020 Report, Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed on January 24, 2021.

Item 45 Answer: D

Educational Objective: Prevent hyperoxia in a critically ill patient.

The patient requires no additional oxygen management (**Option D**). A 2018 systematic review found that supplemental oxygen in patients with normal oxygen saturation increases mortality. This review focused on acutely ill adults with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery. In the liberal oxygen therapy group, the median baseline oxygen saturation as measured by pulse oximetry (Spo_2) was 96% with a range of 94% to 99%. Compared with the conservative oxygen therapy group, patients with the highest Spo_2 had increased in-hospital mortality, increased 30-day mortality, and increased mortality at longest follow-up. A dose-response curve was evident, with mortality highest in trials with the greatest increase in Spo_2. Providing supplemental oxygen for patients with an Spo_2 higher than 96% increased mortality by approximately 1%. Based on these results, an international expert panel provided two strong recommendations: (1) an Spo_2 of 96% or lower should be maintained in patients receiving oxygen therapy, and (2) oxygen therapy should not be started for patients with acute myocardial infarction or stroke and an Spo_2 of 93% or higher. These guidelines do not apply to all acute medical conditions. For example, higher Sao_2 values of nearly 100% are likely beneficial for patients with carbon monoxide poisoning, cluster headache, sickle cell crisis, or pneumothorax.

A nonrebreather mask (**Option A**) is an oxygen delivery method that uses a mask, an oxygen reservoir, and a system of one-way valves that limits the mixing of the oxygen supply with exhaled gases and room air. As a short-term solution for significant hypoxemia, it supplies the highest concentration of oxygen (95%) that can be provided to a spontaneously breathing patient. This patient has no indication for delivery of such high concentrations of oxygen, and this therapy could prove to be detrimental for the patient.

Venturi masks (**Option B**) consist of a device that mixes air and oxygen. The flow of oxygen through the device entrains air, which results in a consistent inhaled oxygen concentration. Venturi masks are indicated for patients in whom fixed oxygen concentrations are desired. This patient has no indication for oxygen therapy by any means, including Venturi mask.

The patient has normal oxygen saturation. Oxygen, 3 L/min by nasal cannula (**Option C**), is not indicated for this patient and may increase mortality if use results in increased Spo_2 above 96%.

KEY POINT

- Providing supplemental oxygen in acutely ill medical patients with normal oxygen saturation increases mortality in a dose-dependent manner.

Bibliography

Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ. 2018;363:k4169. [PMID: 30355567] doi:10.1136/bmj.k4169

Item 46 Answer: B

Educational Objective: Diagnose obstructive sleep apnea after anesthesia.

The most likely cause of the patient's hypoxemia is obstructive sleep apnea (OSA) (**Option B**). OSA may be clinically recognized for the first time after a procedure that entails general anesthesia and/or narcotics. In this situation, OSA may manifest as repeated episodes of postoperative hypoxemia but may also present as frank respiratory failure. This patient has risk factors for OSA, including obesity, male sex, hypertension, and a thick neck. Many of these risk factors are incorporated into predictive scoring algorithms to identify those individuals before surgery. With increasing use of screening tools and perioperative care pathways, unexpected patient events due to undiagnosed OSA following general anesthesia or opioid analgesics are less common than in the past.

Aspiration pneumonia (**Option A**) is less likely after an elective surgical procedure, which is usually preceded by precautions to avoid oral intake for several hours before surgery. The normal chest radiograph after intubation and postintubation normalization of hypoxemia also rule out aspiration as a cause of acute respiratory failure.

Pulmonary edema (**Option C**), atelectasis, and pneumonia are among the most common reasons for reintubation following general anesthesia. These conditions would be associated with an abnormal postintubation chest radiograph and would not quickly resolve with intubation and mechanical ventilation, making them unlikely diagnoses.

The risk for postoperative deep venous thromboembolism (VTE) is highest after 48 to 72 hours of immobilization; most postorthopedic surgery care pathways, including prolonged anticoagulation as seen in this patient, are designed to prevent VTE. Pulmonary embolism (**Option D**) immediately after orthopedic surgery would be unusual, as would complete resolution of hypoxemia immediately after intubation.

KEY POINT

- Obstructive sleep apnea may be clinically recognized for the first time after a procedure that entails general anesthesia and/or narcotics and may manifest as repeated episodes of postoperative hypoxemia but may also present as frank respiratory failure.

Bibliography

Tamisier R, Fabre F, O'Donoghue F, et al. Anesthesia and sleep apnea. Sleep Med Rev. 2018;40:79-92. [PMID: 29174558] doi:10.1016/j.smrv.2017.10.006

Item 47 Answer: C

Educational Objective: Evaluate a pulmonary nodule with an integrated PET/CT scan.

An integrated PET/CT (**Option C**) should be performed next. PET utilizes the radionuclide 18-fluoro-2-deoxyglucose, which accumulates within highly metabolically active cells such as cancer cells and can be visualized as discrete areas of uptake. Integrated PET/CT allows improved localization of the metabolic activity. PET scans are widely used to evaluate risk of malignancy in lung nodules, to stage known thoracic tumors, and to evaluate for metastatic disease from other nonthoracic malignancies. False-positive PET scans can occur in other hypermetabolic conditions, such as infection or inflammation, in which cells accumulate fluorodeoxyglucose. False-negative results can occur when tumors have low rates of metabolic activity, such as carcinoid, adenocarcinoma in situ, and, rarely, metastatic kidney, prostate, or testicular cancer. PET is not useful in determining malignancy in lung nodules less than 8 mm in size; however, a PET/CT scan can help in staging and needle positioning for biopsy targets. For example, in this patient with a solitary pulmonary nodule, a PET/CT scan may help determine whether any lymph node involvement is present that was not visible on the chest CT scan, providing a potentially more accessible and strategically important biopsy target.

Endobronchial ultrasound (EBUS) (**Option A**) permits visualization of mediastinal and hilar lymph nodes for needle aspiration. EBUS with transbronchial needle aspiration is the initial procedure for obtaining tissue from mediastinal and hilar lymph nodes in the diagnosis and staging of patients with known or suspected thoracic malignancy. An integrated PET/CT scan can guide where to biopsy, and it would be premature to perform an EBUS-guided transbronchial needle aspiration without this information.

For patients suspected of having interstitial lung disease, a high-resolution (slice thickness of 1 mm) CT (**Option B**) should be ordered. However, because the slice interval (the distance between individual slices) with high-resolution CT is larger than with conventional CT, this technique "skips" interval sections of the lung and should not be used to evaluate lung nodules. A high-resolution CT scan cannot stage lung cancer or guide where to biopsy.

Sputum cytology (**Option D**) has a lower sensitivity than EBUS-guided transbronchial needle aspiration for diagnosis of lung cancer, does not produce sufficient sample material for molecular studies, and will not provide needed staging information.

KEY POINTS

- PET/CT scans are widely used to evaluate risk of malignancy in lung nodules, to stage known thoracic tumors, and to evaluate for metastatic disease from other nonthoracic malignancies.
- PET scans are not useful for determining malignancy in lung nodules less than 8 mm in size.

Bibliography

Colarinha P. Why and when to request for A Pet/Ct scan in A lung cancer patient? Rev Port Cir Cardiotorac Vasc. 2020 Jul-Sep;27:167-177. [PMID: 33068505]

Item 48 Answer: C

Educational Objective: Treat acute respiratory distress syndrome with prone positioning.

The most appropriate management is prone positioning (**Option C**). The patient has severe acute respiratory distress syndrome (ARDS) due to influenza pneumonia (arterial $Po_2/Fio_2 = 92$). Prone positioning reduces compression of portions of the lung behind the cardiac and mediastinal structures and improves ventilation/perfusion matching in patients with ARDS. Prone positioning for at least 12 to 16 hours daily should be considered for patients with moderate to severe ARDS with persistent hypoxemia despite use of low tidal volume ventilation and plateau pressure less than 30 cm H_2O. The indications for prone positioning have been variably defined, but entry criteria in a pivotal clinical trial that showed benefit included: arterial $Po_2/Fio_2 <150$; $Fio_2 \geq 0.60$ on positive end-expiratory pressure >5 cm H_2O. Study participants were intubated for less than 48 hours before initiating prone positioning. Although the patient is also meeting goals for lung protective ventilation, randomized trials show that the addition of prone positioning improves mortality in those patients.

The sedation level should not be increased (**Option A**). The patient is meeting goals for sedation and is calm and easily arousable. Light-sedation protocols or daily awakening trials are associated with decreased length of mechanical ventilation and length of ICU stay.

In patients with refractory hypoxemia, a recruitment maneuver (**Option B**)—applying a high level of CPAP to open collapsed alveoli (e.g., continuous pressure to 35 cm H_2O for 40 seconds)—has been conditionally recommended. However, a randomized control trial demonstrated that recruitment maneuvers in patients with moderate to severe ARDS was associated with increased risk for barotrauma, pneumothorax, and death compared with standard care.

The FACCT trial suggested that excessive fluid resuscitation is harmful to ARDS patients. This trial compared conservative with liberal fluid strategies based on central venous pressure and pulmonary artery occlusion pressure (a surrogate for left atrial pressure) in patients with ARDS. Although mortality did not differ between groups, patients who were treated with conservative fluid management showed improved oxygenation and decreased time on the ventilator and in the ICU. In patients who are hemodynamically stable and do not have end-organ hypoperfusion, minimizing fluid administration is warranted. This patient still requires norepinephrine blood pressure support; diuresis is not indicated at this time (**Option D**).

KEY POINT

- Prone positioning for at least 12 hours daily should be considered for patients with acute respiratory syndrome and arterial Po_2/Fio_2 <150 mm Hg, Fio_2 ≥0.60 on positive end-expiratory pressure >5 cm H_2O, who have been intubated for less than 48 hours.

Bibliography

Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562-572. [PMID: 28792873] doi:10.1056/NEJMra1608077

Item 49 Answer: B

Educational Objective: Treat obesity hypoventilation syndrome.

The most appropriate treatment is bilevel positive airway pressure (BPAP) (**Option B**). The patient has hypercapnic respiratory failure due to a combination of opiates (oxycodone) and obesity hypoventilation syndrome (OHS), in which the obesity has led to mechanical changes that increase the load that the respiratory muscles must overcome. The addition of opiates decreased the respiratory drive in a patient that had underlying hypoventilation. BPAP delivers a higher level of positive airway pressure during inspiration than during expiration. In the acute setting, the difference between expiratory and inspiratory pressure helps the respiratory muscles generate appropriate tidal volumes. A backup respiratory rate can also be designated to initiate breaths in patients who have a low respiratory rate. The 2019 guidelines from the American Thoracic Society (ATS) recommend that hospitalized patients suspected of having OHS should be started on noninvasive ventilation with either BPAP or volume-targeted pressure support and continued on this therapy until they undergo outpatient evaluation for obstructive sleep apnea (OSA), ideally during the first 3 months after hospital discharge.

Acetazolamide (**Option A**) is a respiratory stimulant that has been used to improve ventilation in patients with OHS. However, it does not address concurrent obstructive sleep apnea and can lead to electrolyte abnormalities. Acetazolamide may be considered as an adjuvant treatment in patients with refractory OHS who continue to hypoventilate even with noninvasive ventilation and weight loss.

The ATS recommends CPAP (**Option C**) rather than BPAP as the initial treatment for stable ambulatory adult patients with OHS and concurrent severe OSA. Importantly, since more than 70% of patients with OHS have severe OSA, the diagnosis should be confirmed by polysomnography in a sleep laboratory. Until that time, the ATS recommends that patients with OHS be treated with either BPAP or volume-targeted pressure support.

Intubation and invasive mechanical ventilation (**Option D**) are an option in the care of patients with acute exacerbation of OHS. However, this patient can be aroused and has no contraindications to BPAP. Thus, a time-limited trial (1-2 hours) of BPAP, with repeated evaluation of gas exchange, is warranted.

KEY POINTS

- Hospitalized patients suspected of having obesity hypoventilation syndrome should be started on noninvasive ventilation with either bilevel positive airway pressure or volume-targeted pressure support.
- More than 70% of patients with obesity hypoventilation syndrome have severe obstructive sleep apnea; the diagnosis should be confirmed with polysomnography in a sleep laboratory.

Bibliography

Mokhlesi B, Masa JF, Brozek JL, et al. Evaluation and management of obesity hypoventilation syndrome. an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2019;200:e6-e24. [PMID: 31368798] doi:10.1164/rccm.201905-1071ST

Item 50 Answer: B

Educational Objective: Treat severe COPD with roflumilast.

The most appropriate treatment is roflumilast (**Option B**). This patient has COPD with Global Initiative for Chronic Obstructive Lung Disease (GOLD) class D severity based on his high symptom burden and exacerbations. He is already receiving combination inhaled therapy with a long-acting β_2-agonist, long-acting muscarinic antagonist, and inhaled glucocorticoid. Roflumilast, a selective phosphodiesterase-4 inhibitor, can reduce symptoms and exacerbations in patients with severe COPD who have a chronic bronchitis phenotype or frequent exacerbations. Given this patient's clinical picture, he would likely benefit from the addition of roflumilast. Azithromycin, a macrolide antibiotic, can also be used for patients with COPD and persistent exacerbations, especially in those who are current nonsmokers. There are no head-to-head comparisons of roflumilast with azithromycin. The choice of medication is determined by the medication's side effects, drug interactions, and contraindications.

Nocturnal noninvasive ventilation with bilevel positive airway pressure (**Option A**) can be prescribed for patients with concomitant obstructive sleep apnea or chronic hypercapnic respiratory failure (Pco_2 of 52 mm Hg [6.9 kPa] or higher). In select populations, it may improve hospital-free survival. This patient does not meet the criteria for nocturnal noninvasive ventilation.

For patients with COPD, supplemental oxygen therapy (**Option C**) improves quality of life and decreases mortality in patients with an arterial Po_2 of 55 mm Hg (7.3 kPa) or less or an oxygen saturation as measured by pulse oximetry of 88% or less. For patients with COPD who also have cor pulmonale, heart failure, or erythrocytosis, these thresholds are lowered to a Po_2 of 59 mm Hg (7.8 kPa) or less or oxygen saturation of 89% or less. However, this patient does not meet these criteria.

Because this patient will likely benefit from the addition of roflumilast, discharging him with no additions to his treatment regimen (**Option D**) would not be appropriate.

KEY POINT

- Roflumilast, a selective phosphodiesterase-4 inhibitor, can reduce symptoms and exacerbations in patients with severe COPD who have a chronic bronchitis phenotype or frequent exacerbations.

Bibliography

Labaki WW, Rosenberg SR. Chronic obstructive pulmonary disease. Ann Intern Med. 2020;173:ITC17-ITC32. [PMID: 32745458] doi:10.7326/AITC202008040

Item 51 Answer: B

Educational Objective: Evaluate possible lung cancer with a chest CT.

The most appropriate next step in management is CT of the chest (**Option B**). The patient presents with a chest mass in the superior sulcus that has led to shoulder and arm pain, weakness and atrophy of the muscles of the hand, and Horner syndrome (ptosis, miosis, anhidrosis). This constellation of symptoms is called Pancoast syndrome and is typically caused by tumor infiltration of the brachial plexus and/or extension of the tumor into the parietal pleural, ribs, or vertebral bodies. These tumors are typically non–small cell lung cancer (NSCLC) and do not present with symptoms of dyspnea or cough until late because of their peripheral location. Diagnosis of these tumors can be delayed by several months because patients may first be treated for shoulder bursitis or arthritis. Superior sulcus tumors are staged the same way as NSCLC elsewhere in the chest. Initial evaluation should start with a full history, physical examination, complete blood count, serum chemistry studies, and CT of the chest. The presence of findings on physical examination (consolidation, effusion, bone tenderness, neurologic findings) will indicate advanced disease. PET can be very helpful in the initial evaluation of potential lung cancer, as several studies have demonstrated that PET identifies unsuspected mediastinal involvement, distant disease, or both, which informs staging biopsies and reduces futile (noncurative) surgery. The definitive diagnosis of lung cancer requires tissue histopathology. In patients with radiographic evidence of advanced stage disease, diagnosis and staging are best accomplished with a single invasive test at a location that will establish both the diagnosis and the stage of disease.

Bronchoscopy (**Option A**) is not a good choice for two reasons. First, to assess accessibility for biopsy, a CT should be performed first. Second, in this patient the tumor is a peripheral lesion, and the yield for peripheral lesions is typically low. Even if the lesion were accessible by bronchoscopy, it may not be the best modality if it cannot simultaneously diagnose and stage the tumor.

CT-guided biopsy (**Option C**) is not the best choice because there has been no assessment for possible metastatic disease. Ideally, one biopsy should be performed for both staging and diagnosis.

Surgical resection (**Option D**) should not be performed until the extent of disease has been determined. Chest CT, as an initial investigation, would help determine the presence of metastatic disease within the thorax and potential resectability of the tumor.

KEY POINT

- In patients with radiographic evidence of advanced stage lung cancer, diagnosis and staging are best accomplished with a single invasive test at a location that will establish both the diagnosis and the stage of disease.

Bibliography

Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. Mayo Clin Proc. 2019;94:1623-1640. [PMID: 31378236] doi:10.1016/j.mayocp.2019.01.013

Item 52 Answer: B

Educational Objective: Manage an abnormal pulse oximetry reading.

The most appropriate management is to change the pulse oximetry probe to an earlobe probe (**Option B**). Pulse oximetry calculates the differential between absorption of infrared light by oxygenated and deoxygenated blood and is widely used to monitor oxygenation. Conventional probes used on the finger, toe, and earlobe rely on transmission technology, utilizing emitting and detecting sensors applied on opposing sides of the digit or earlobe. Inaccurate readings can be caused by vasoconstriction, low perfusion states, skin pigmentation, motion artifact, or nail polish. The clinician should examine the pulse oximeter waveform to determine if the reading is accurate; a normal signal shows a sharp waveform with a clear dicrotic notch. The absence of a clear dicrotic notch suggests the device is not providing an accurate reading. In a patient with Raynaud phenomenon and clinical signs of peripheral vasoconstriction, pulse oximetry with a finger probe is likely to be erroneous. Options include changing to an earlobe probe or use of reflectance technology with a forehead probe in which the emitter and detector sensors are adjacent to each other.

Increasing the oxygen therapy to an $\mathrm{F_{IO_2}}$ of 0.50 (**Option A**) would be appropriate only after pulse oximeter has been verified for accuracy. A 2018 systematic review found that supplemental oxygen in patients with normal oxygen saturation increases mortality. The review focused on acutely ill adults with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery.

Arterial blood gases (ABGs) (**Option C**) should be measured to assess for underlying hypercapnia in patients with a low $\mathrm{FEV_1}$, a change in mental status, acute COPD or asthma exacerbations, elevated level of serum bicarbonate, or in some patients, oxygen desaturation on pulse oximetry. Before ABGs are obtained in this patient, the pulse oximetry reading needs to be verified by replacing the finger probe with an earlobe or forehead probe.

CONT.

CT angiography (**Option D**) has significantly improved the accuracy of evaluating pulmonary embolism. For patients who present with symptoms suspicious for an acute venous thromboembolism (VTE), such as sudden drop in oxygenation, CT angiography provides a rapid, noninvasive means of diagnosis. Initiating an evaluation for VTE in this patient should be considered only if the pulse oximetry reading is verified to be accurate.

KEY POINTS

- Inaccurate pulse oximetry reading by finger probe can be caused by vasoconstriction, low perfusion states, skin pigmentation, motion artifact, or nail polish.
- In cases of suspected inaccurate pulse oximetry by finger probe, changing to an earlobe probe or forehead probe is indicated.

Bibliography

Jubran A. Pulse oximetry. Crit Care. 2015;19:272. [PMID: 26179876] doi:10.1186/s13054-015-0984-8

Item 53 Answer: C

Educational Objective: Treat gastrointestinal bleeding with packed red blood cell transfusion.

The most appropriate treatment for this patient is transfusion of packed red blood cells (PRBCs) (**Option C**). He is likely experiencing acute upper gastrointestinal bleeding from a variceal hemorrhage with subsequent hypovolemia and hypotension. In patients with cirrhosis, variceal hemorrhage carries a significant risk of morbidity and mortality. Studies have demonstrated that the mortality rate is decreased with a restrictive transfusion strategy, defined as a hemoglobin goal of 7 to 9 g/dL (70-90 g/L), compared with a liberal transfusion strategy. However, different thresholds and hemoglobin levels may trigger transfusion in actively bleeding patients who are in shock. Higher hemoglobin values may also be desirable in patients with acute coronary syndrome or chronic cardiovascular disease. In patients with portal hypertension, transfusion to higher values (10 g/dL [100 g/L] or higher) can rapidly increase portal pressure, putting the patient at significant risk for rebleeding. In addition to PRBCs, early resuscitation with crystalloid fluids is indicated to provide vascular support while waiting for blood products.

During massive variceal bleeding in which endoscopic care is delayed or it is impossible to visualize the bleeding source, balloon tamponade (**Option A**) is an option. However, balloon tamponade carries several risks, including esophageal rupture and ulceration, and should be used only in cases of life-threatening hemorrhage and only until alternative hemostasis methods can be employed. Although this patient has evidence of acute upper gastrointestinal bleeding, the source of the bleeding is not yet identified and clinical findings do not indicate uncontrolled bleeding.

In patients with hypovolemic shock, vasopressors such as norepinephrine (**Option B**) are usually not helpful since they do not correct the primary underlying problem and, in the absence of adequate volume resuscitation, further reduce tissue perfusion.

Transjugular intrahepatic portosystemic shunt (TIPS) (**Option D**) can help in managing acute variceal bleeding and preventing recurrent variceal hemorrhage. In patients without previous variceal hemorrhage, hemostasis should be attempted with pharmacologic and endoscopic methods first. If this fails, TIPS should be considered.

KEY POINTS

- Most patients with acute upper gastrointestinal bleeding should receive a transfusion of packed red blood cells to a target hemoglobin level of 7 to 9 g/dL (70-90 g/L).
- In patients with portal hypertension and acute gastrointestinal bleeding, transfusion to 10 g/dL (100 g/L) or higher can rapidly increase portal pressure, putting the patient at significant risk for rebleeding.

Bibliography

Siau K, Hearnshaw S, Stanley AJ, et al. British Society of Gastroenterology (BSG)-led multisociety consensus care bundle for the early clinical management of acute upper gastrointestinal bleeding. Frontline Gastroenterol. 2020;11:311-323. [PMID: 32582423] doi:10.1136/flgastro-2019-101395

Item 54 Answer: C

Educational Objective: Treat ethylene glycol poisoning.

The most appropriate treatment is fomepizole and hemodialysis (**Option C**). The patient probably has ethylene glycol toxicity. Fomepizole blocks the enzyme alcohol dehydrogenase, which converts alcohols such as ethylene glycol and methanol to their toxic metabolites. Indications for hemodialysis for the ingestion of ethylene glycol or methanol include severe anion gap metabolic acidosis and end-organ involvement (kidney impairment, visual changes). Hemodialysis removes the parent alcohol and its toxic metabolites. It should be performed as soon as possible in confirmed ethylene glycol or methanol poisoning or in suspected cases associated with increased anion gap metabolic acidosis or symptoms of end organ damage. Toxic alcohol ingestion is typically confirmed by drug level measurements, which can take hours to days; hemodialysis would be appropriate now because this patient's presentation is highly suggestive: ethylene glycol is found in automotive coolants; the patient has severe acidemia with an anion gap of 22 and normal glucose and lactate levels; and the osmolal gap is elevated.

Ethanol (**Option A**) blocks alcohol dehydrogenase by competing with other alcohols. Although administration of ethanol is effective for toxic alcohol poisoning, it is limited by imprecise dosing, which can lead to the typical adverse effects of ethanol intoxication (e.g., sedation and behavioral disinhibition). Fomepizole (**Option B**) is therefore preferable to ethanol for this purpose because its dosing is precise and it lacks the adverse effects of ethanol. Fomepizole is expensive, however, and may not be as widely available as ethanol.

Because ethylene glycol or methanol intoxication can cause sedation similar to that seen with ethanol intoxication, sedative drugs such as lorazepam (**Option D**) are generally avoided in patients with alcohol intoxication. However, in ethanol ingestion the patient should be monitored for alcohol withdrawal, which can be fatal. Treatment of alcohol withdrawal with benzodiazepines such as lorazepam is appropriate.

KEY POINTS

- Ethylene glycol and methanol toxicity should be treated with fomepizole.
- Indications for hemodialysis in the setting of ethylene glycol or methanol toxicity include severe anion gap metabolic acidosis and end-organ involvement (kidney impairment, visual changes).

Bibliography

Kraut JA, Mullins ME. Toxic alcohols. N Engl J Med. 2018;378:270-280. [PMID: 29342392] doi:10.1056/NEJMra1615295

Item 55 Answer: C

Educational Objective: Assess need for critical care placement in a patient at high risk for sepsis.

The most appropriate venue for care of this patient is the ICU (**Option C**). There are no universally accepted criteria for admission to an ICU. Signs and symptoms of clinical instability, including hypotension, hypoxemia, arrhythmias, and mental status changes, may be useful to identify patients who require intense resources or may be at risk of sudden deterioration. This patient has many findings to suggest clinical instability, including abnormal oxygen saturation, borderline hypotension, tachycardia, tachypnea, and altered mental status. Sepsis-3 guidelines recommend the use of the quick Sequential Organ Failure Assessment (qSOFA) score, a simplified clinical scoring system that includes only three criteria: respiration rate of 22/min or greater, altered mentation, and systolic blood pressure 100 mm Hg or less. A qSOFA score of 2 or greater in the setting of known or suspected infection is used to predict increased mortality and should prompt evaluation for resuscitation and consideration of ICU admission. Recently, the use of qSOFA to predict sepsis has come under increased scrutiny given conflicting studies regarding its accuracy across different patient populations. Other scoring systems, such as the National Early Warning System (NEWS), may outperform qSOFA in predicting in-hospital death and need for ICU admission. Because there is no perfect test for identifying sepsis, scoring systems should not be used as the sole indicator of disease or triage needs.

This patient has evidence of clinical instability, including borderline abnormal oxygen saturation, hypotension, tachycardia, tachypnea, and altered mental status. She is at risk of rapid clinical deterioration. Managing this patient in sites other than the ICU, including the emergency department observation unit (**Option A**), general medicine ward (**Option B**), or an outpatient setting (**Option D**), places her at risk if there is a sudden change in clinical status in a setting that is unable to respond with the necessary personnel and resources for quick and effective resuscitation.

KEY POINT

- Signs and symptoms of clinical instability, including hypotension, hypoxemia, arrhythmias, and mental status changes, may be useful in identifying those patients who require intense resources or may be at risk of deterioration.

Bibliography

Liu VX, Lu Y, Carey KA, et al. Comparison of early warning scoring systems for hospitalized patients with and without infection at risk for in-hospital mortality and transfer to the intensive care unit. JAMA Netw Open. 2020;3:e205191. [PMID: 32427324] doi:10.1001/jamanetworkopen.2020.5191

Item 56 Answer: C

Educational Objective: Diagnose cystic fibrosis.

The most likely diagnosis is cystic fibrosis (CF) (**Option C**). Cystic fibrosis is an autosomal recessive genetic disorder affecting the *CFTR* gene. The most common genetic variant resulting in disease is ΔF508. The abnormal *CFTR* genotype results in abnormally thick secretions that are difficult to clear. These secretions lead to chronic bacterial infection and inflammation in the lungs, which eventually lead to bronchiectasis. Pulmonary symptoms include chronic productive cough, recurrent sinusitis, and recurrent pulmonary infections. Many patients also develop liver disease (from impaired bile flow), endocrine and exocrine pancreatic insufficiency, and malabsorption. Male infertility is common. CF is most commonly diagnosed in children after an abnormal newborn screening but is sometimes not diagnosed until adulthood. Sweat chloride testing is the initial test for CF, with genetic testing confirming the diagnosis.

Allergic bronchopulmonary aspergillosis (ABPA) (**Option A**) is an ongoing immunologic response to inhaled *Aspergillus* species that leads to persistent eosinophilic airway inflammation, increased IgE levels (both total and *Aspergillus* specific), and eventually tissue damage with airway remodeling. Patients present with difficult-to-control asthma, productive cough, and expectoration of brownish mucus plugs. Radiographs may demonstrate pulmonary infiltrates and bronchiectasis. The normal immunoglobulin levels and presence of chronic diarrhea make ABPA an unlikely diagnosis in this patient.

In α_1-antitrypsin deficiency (**Option B**), proteases that would normally be inactivated by antiproteases (e.g., α_1-antitrypsin) lead to destruction of lung tissue. This condition most commonly leads to emphysema, although bronchiectasis can also occur. However, this condition is unlikely given the patient's constellation of pulmonary, sinus, and gastrointestinal symptoms and lack of emphysematous changes on chest imaging.

Although selective IgA deficiency (**Option D**) is the most common primary antibody deficiency, most patients remain asymptomatic. IgA provides mucosal immunity; therefore, patients with IgA deficiency are susceptible to infections of the respiratory tract and, less frequently, gastrointestinal tract. Sinopulmonary infections are the most common presenting manifestation. Patients with IgA deficiency may also develop celiac disease with associated chronic diarrhea. Consideration of IgA deficiency is reasonable in this patient, but immunoglobulin testing is normal, excluding this disorder.

KEY POINTS

- The diagnosis of cystic fibrosis should be considered in young adults with any symptom or combination of symptoms such as chronic productive cough, recurrent sinusitis, recurrent pulmonary infections, and bronchiectasis.
- Sweat chloride testing is the initial test for cystic fibrosis, with genetic testing confirming the diagnosis.

Bibliography

Boucher RC. Muco-obstructive lung diseases. N Engl J Med. 2019;380:1941-1953. [PMID: 31091375] doi:10.1056/NEJMra1813799

Item 57 Answer: B

Educational Objective: Treat refractory septic shock with glucocorticoid therapy.

The most appropriate additional management is intravenous administration of hydrocortisone (**Option B**). This patient has septic shock related to the necrotic diabetic foot ulcer. Despite aggressive early resuscitation with crystalloid fluids and concomitant vasopressors, the patient's hemodynamic status remains unstable. The use of glucocorticoids in the setting of sepsis has been suggested to achieve hemodynamic stability when it is not achieved with intravenous fluids and vasopressor therapies. A 2018 meta-analysis of 42 trials concluded that although there was no evidence that glucocorticoids improve mortality, patients with septic shock who receive glucocorticoids are more likely to have reversal of shock within 7 days. Guidelines published by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine in 2017 recommend consideration of glucocorticoids for patients with refractory septic shock at a maximum dose of 400 mg hydrocortisone daily or the equivalent using another glucocorticoid. The 2016 Surviving Sepsis Campaign guidelines recommend hydrocortisone in doses up to 200 mg daily for refractory shock.

Several studies have evaluated the utility of assessing endogenous cortisol levels and cortisol reserves in patients with shock. Historically, utilization of cosyntropin stimulation (**Option A**) was widespread. However, failure to demonstrate correlation between baseline cortisol level or cortisol reserve and response to glucocorticoid supplementation does not support use of this measurement in patients with refractory shock.

Guidelines recommend against the use of intravenous immunoglobulins (IVIG) (**Option C**) in patients with sepsis or septic shock. Individual randomized studies and systematic reviews and meta-analyses have failed to convincingly demonstrate that the use of IVIG results in reduced mortality and are not recommended.

Procalcitonin measurement (**Option D**) should not be ordered in this patient. Its use as a therapeutic guide for initiation of antibiotics in septic patients or as a way to determine the source of infection in critical illness has been studied with conflicting results. The most robust data have been shown when procalcitonin levels were used to guide antibiotic deescalation in patients with lower respiratory tract infection. Since the test would not help guide the management of this patient's refractory shock, it is not indicated.

KEY POINTS

- The use of glucocorticoids in the setting of sepsis is suggested if adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability.
- Guideline-recommended hydrocortisone dosage for refractory septic shock varies from a maximum of 200 mg to 400 mg daily.

Bibliography

Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. Crit Care Med. 2018;46:1411-1420. [PMID: 29979221] doi:10.1097/CCM.0000000000003262

Item 58 Answer: D

Educational Objective: Treat depression associated with montelukast.

The most appropriate treatment is to stop montelukast (**Option D**). After initiation of asthma therapies, patients should be reassessed for symptom control and medication tolerance. Montelukast has been associated with significant adverse mental health effects and may be the cause of the patient's depression. Depressive symptoms can occur in patients with and without a previous history of depression or other neuropsychiatric disorders. In March 2020 the FDA added a boxed warning to montelukast, strengthening previous warnings about behavior and mood-related changes, including suicides, associated with this medication. The FDA also advised against using montelukast for allergic rhinitis because other first-line medications, such as intranasal glucocorticoids, are widely available and more efficacious and because many physicians are unaware of montelukast's potential adverse mental health effects. This patient's asthma symptoms are well controlled, and he has new symptoms and a positive Patient Health Questionnaire-2 result suggesting depression; therefore, montelukast should be discontinued, and the patient should be monitored for improvement in his depressive symptoms, which typically resolve if medication related. Other adverse effects include anaphylaxis, angioedema, dizziness, dyspepsia, muscle weakness, and elevated transaminases occurring in less than 2% of all patients. The occurrence of eosinophilic granulomatosis with polyangiitis has been described in patients taking antileukotriene agents, but most cases occur following discontinuation of glucocorticoids for severe asthma and may simply represent an uncovering of a previously undiagnosed condition. It remains unclear if this adverse event is caused by the drug.

Escitalopram (**Option A**) is a selective serotonin reuptake inhibitor used to treat depression and anxiety in adults. Adding an antidepressant to this patient's regimen is not necessary because the montelukast may be the cause of the patient's depression and discontinuation of the medication may resolve his symptoms.

Controller medications such as salmeterol or budesonide-formoterol (**Options B, C**) can be stepped up or down with the goal of maintaining symptom control and minimizing medication exposure. Stepping up this patient's treatment regimen with additional controller medications is not indicated because his asthma symptoms are well controlled. Instead, his therapy should be stepped down, and the first drug to be discontinued is montelukast.

KEY POINTS

- After initiation of asthma therapies, patients should be reassessed for symptom control and medication tolerance.
- Montelukast should be discontinued in patients with symptoms suggestive of depression.

Bibliography

Voelker R. Boxed warning for allergy drug. JAMA. 2020;323:1236. [PMID: 32259219] doi:10.1001/jama.2020.4040

Item 59 Answer: B

Educational Objective: Manage intravenous access for patients in shock.

For this patient, the most appropriate additional intravenous (IV) access is a second 18-gauge peripheral IV catheter in the arm (**Option B**). The patient has developed hemorrhagic shock. Patients with osteogenesis imperfecta have an increased propensity for bleeding due to dysfunctional interactions between platelets and endothelial cells. In addition, collagen defects can lead to increased fragility of capillary beds. Patients with hemorrhagic shock should be managed with volume repletion, and IV crystalloid solution should be initiated while waiting for blood products. This patient has a single peripheral IV with which to start resuscitation, but a second access point should be obtained in case the first IV becomes dysfunctional. According to the law of Poiseuille, the flow of fluid through a tube is dictated in part by the radius and length of the tube. If we apply this to venous access catheters, choosing a device that is short and has a wide diameter lumen will maximize flow rates through the catheter for volume resuscitation.

Although a peripherally inserted central catheter (PICC) line (**Option A**) or triple-lumen catheter (**Option D**) might seem more durable than a peripheral IV line, their long length and narrow-gauge lumens significantly limit the maximal flow rate of infused fluids. In fact, most 18-gauge IV catheters have a maximal flow rate that far exceeds that of a PICC line and is comparable to that of all three catheters combined in a triple-lumen catheter. In addition, femoral insertion of IV catheters should be avoided if possible due to increased risk of infection and thrombosis.

Intraosseous administration of fluid (**Option C**) is most commonly indicated when IV access is not available. In many situations, placement of an intraosseous needle device in the humerus or tibia is easy, and its short, large-bore lumen allows for rapid administration of IV fluids. However, this patient has IV access, and the device is contraindicated in patients with conditions such as osteogenesis imperfecta, osteopenia, and osteoporosis because placement of the needle may increase fracture risk. In addition, placement of a needle in a bone that is fractured or has already been accessed, or where a previous intraosseous device placement was recently performed, is contraindicated. An 18-gauge peripheral IV line has similar maximal flow rates and is preferred in this patient.

KEY POINT

- For rapid and large-volume fluid administration, choosing an access device that is short and has a wide-diameter lumen will maximize flow rates.

Bibliography

Berman DJ, Schiavi A, Frank SM, et al. Factors that influence flow through intravascular catheters: the clinical relevance of Poiseuille's law. Transfusion. 2020;60:1410-1417. [PMID: 32643172] doi:10.1111/trf.15898

Item 60 Answer: A

Educational Objective: Diagnose ascending cholangitis.

The most likely diagnosis is acute ascending cholangitis (**Option A**). The presence of cholangitis is heralded by the onset of the Charcot triad (fever, jaundice, and right-upper-quadrant abdominal pain) or Reynolds pentad (Charcot triad plus hypotension and altered mental status), as seen in this patient. Diagnostic imaging revealing signs of biliary obstruction further supports the diagnosis. Cholangitis is potentially life-threatening. Initial risk stratification, based on severity and multiplicity of involvement of other organ systems, is used to guide treatment of acute ascending cholangitis. In this patient, aggressive crystalloid resuscitation and antibiotic therapy targeting gram-negative *Enterobacteriaceae* should be administered. Identified common bile duct stones should be removed urgently,

CONT.

with endoscopic retrograde cholangiopancreatography in patients with cholangitis, after which elective cholecystectomy should be performed during the initial hospitalization or within 2 weeks to reduce the risk of complications. In patients who are not surgical candidates, endoscopic sphincterotomy can be performed to facilitate the passage of additional common bile duct stones.

Acute cholecystitis (**Option B**) can also present with fever and abdominal pain, and laboratory studies may show leukocytosis; liver chemistries are not elevated in uncomplicated acute cholecystitis. The diagnosis can be made by ultrasonography showing gallbladder wall thickening and/or edema, which is not present in this patient.

The diagnosis of acute pancreatitis (**Option C**) requires two of the following three criteria: (1) acute-onset abdominal pain characteristic of pancreatitis (severe, persistent for hours to days, and epigastric in location, often radiating to the back); (2) serum lipase or amylase levels elevated to three to five times the upper limit of normal; and (3) characteristic radiographic findings on contrast-enhanced CT. This patient's presentation of septic shock and cholestasis is not consistent with acute pancreatitis.

Pyogenic liver abscesses (**Option D**) are complications of biliary tract infections or portal venous spread of intra-abdominal infections such as diverticulitis. Patients with pyogenic liver abscesses present with fever and right-upper-quadrant abdominal pain. An abscess can typically be detected with ultrasonography. The patient's presentation does not fit the clinical picture of pyogenic liver abscess.

KEY POINTS

- The presence of cholangitis is heralded by the onset of fever, jaundice, and right-upper-quadrant abdominal pain.
- Common bile duct stones should be removed urgently with endoscopic retrograde cholangiopancreatography in patients with acute cholangitis.

Bibliography

Manes G, Paspatis G, Aabakken L, et al. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2019;51:472-491. [PMID: 30943551] doi:10.1055/a-0862-0346

Item 61 Answer: C

Educational Objective: **Treat serotonin syndrome.**

The most appropriate treatment is lorazepam (**Option C**) intravenously. This patient has serotonin syndrome. Risk factors for serotonin syndrome include use of selective serotonin reuptake inhibitors and other medications (sometimes more than one) that increase nervous system serotonin activity. This patient takes paroxetine, a selective serotonin reuptake inhibitor. Tramadol and cocaine also increase serotonin release in the central nervous system. Common signs and symptoms of serotonin syndrome include mental status changes, hyperthermia, diaphoresis, tremor, autonomic instability, muscle and ocular clonus, and hyperreflexia. Treatment includes supportive measures, such as avoidance of any further serotonergic agents, and sedation with benzodiazepines to reduce agitation. Sedation blunts autonomic surges and reduces the muscle activity that contributes to hyperthermia. Cyproheptadine, an antihistamine with antiserotonergic activity, is used off-label as an antidote in serotonin syndrome in patients who do not respond to benzodiazepine therapy. Its effectiveness has not been established in clinical trials, and use is based on expert opinion and case series. It is available only in pill and syrup formulations so must be administered orally, which is sometimes a challenge in uncooperative patients.

Because hyperthermia in serotonin syndrome is a consequence of excessive muscle activity, the centrally acting antipyretic acetaminophen (**Option A**) will not affect temperature elevation in this patient. In extreme cases of hyperthermia, intubation and neuromuscular blockade might be indicated.

Fentanyl (**Option B**) is also a serotonin receptor agonist and should be avoided as a sedative-analgesic agent in the patient with serotonin syndrome.

In patients who have taken sympathomimetic agents such as cocaine or amphetamines, benzodiazepines are the cornerstone of therapy for agitation. β-Blocker medications such as propranolol (**Option D**) should be avoided in patients with cocaine toxicity because they block the β-adrenergic receptors and theoretically leave the activated α-receptors unopposed, leading to severe hypertension. In this case, the patient's blood pressure does not require acute intervention, and sedation will probably reduce blood pressure independently.

KEY POINTS

- Common signs and symptoms of serotonin syndrome include mental status changes, hyperthermia, diaphoresis, tremor, autonomic instability, muscle and ocular clonus, and hyperreflexia.
- Treatment of serotonin syndrome includes supportive measures, such as avoidance of any further serotonergic agents, and sedation with benzodiazepines to reduce agitation.

Bibliography

Werneke U, Truedson-Martiniussen P, Wikström H, et al. Serotonin syndrome: a clinical review of current controversies. J Integr Neurosci. 2020;19:719-727. [PMID: 33378846] doi:10.31083/j.jin.2020.04.314

Item 62 Answer: D

Educational Objective: **Diagnose sleep apnea with polysomnography.**

The most appropriate management is polysomnography in a sleep laboratory (**Option D**). Objective testing is required for a diagnosis of obstructive sleep apnea (OSA) and central sleep apnea (CSA). In-laboratory polysomnography is the gold standard test for mission-critical workers, patients with complicated OSA, and patients with comorbid conditions such as heart failure, neuromuscular disease, and advanced pulmonary disease in which diagnostic and treatment algorithms are more complex. This patient has risk factors for both OSA (male sex, snoring, overweight) and CSA (heart failure and atrial fibrillation). Once the type of apnea is clarified during the diagnostic portion of polysomnography, the technician may then use the most appropriate mode of positive airway pressure therapy and assess the response to treatment.

An actigraph (**Option A**), a small device worn on the wrist, uses an accelerometer and an ambient light sensor to objectively measure disrupted sleep patterns and sleep-wake cycles over multiple days and nights. Actigraphy is not a substitute for a home sleep study or polysomnography and cannot diagnose sleep apnea syndromes.

Home sleep apnea testing (**Option B**) should be used in patients without comorbid cardiopulmonary disease who are likely to have OSA of at least moderate severity, such as a middle-aged man with obesity who snores loudly, pauses breathing, and gasps during sleep.

Overnight pulse oximetry (**Option C**) is poorly discriminative to diagnose OSA, but in those who are asymptomatic with a low pretest probability, normal overnight oximetry might be reassuring and support the decision to avoid further testing. The patient has daytime sleepiness, which is a strong indication for treatment of sleep-disordered breathing. Further screening with overnight oximetry will not add reliably important diagnostic information, nor will it alter the decision to treat.

KEY POINT

- In-laboratory polysomnography is the gold standard sleep apnea test for mission-critical workers, patients with complicated obstructive sleep apnea, and patients with comorbid conditions such as heart failure, neuromuscular disease, and advanced pulmonary disease in which diagnostic and treatment algorithms are more complex.

Bibliography

Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13:479-504. [PMID: 28162150] doi:10.5664/jcsm.6506

H Item 63 Answer: C

Educational Objective: Treat COPD with pulmonary rehabilitation.

The most appropriate treatment is pulmonary rehabilitation (**Option C**). This patient has been hospitalized for a COPD exacerbation and is ready for discharge. The most important next step is to optimize her therapy. Pulmonary rehabilitation integrates exercise training, education, and nutritional and social support for patients with chronic lung conditions. It has numerous benefits, including reduced symptoms, improved quality of life, and decreased frequency of hospitalizations, in patients with COPD. Addition of pulmonary rehabilitation is recommended for patients with COPD and moderate to severe symptoms (e.g., having to walk more slowly than others of same age due to breathlessness, having to stop to catch breath when walking on level ground at own pace, or having more severe breathlessness) and for patients experiencing at least one COPD exacerbation per year, particularly in those recently hospitalized after an exacerbation. This patient meets the criteria for pulmonary rehabilitation.

α_1-Antitrypsin augmentation therapy (**Option A**) can slow the progression of emphysema in patients with α_1-antitrypsin deficiency, but it is not effective for the treatment of COPD in patients without α_1-antitrypsin deficiency. An α_1-antitrypsin level should be obtained once in all patients with COPD. If α_1-antitrypsin deficiency is diagnosed, augmentation therapy might be indicated. It would be premature to provide augmentation therapy without first measuring the α_1-antitrypsin level.

The National Emphysema Treatment Trial (NETT) demonstrated that patients with upper-lobe-predominant emphysema and significant exercise limitations even after participation in a pulmonary rehabilitation program had improved quality of life, exercise tolerance, pulmonary function, and survival with lung volume reduction surgery (**Option B**). This patient has homogenous emphysema, and there is no evidence of exercise limitations.

The patient had a minimum oxygen saturation of 89% during a 6-minute walk test. Supplemental oxygen therapy (**Option D**) improves quality of life and decreases mortality for patients with COPD and a Po_2 of 55 mm Hg (7.3 kPa) or less or an oxygen saturation of 88% or less. For patients with COPD and certain comorbidities such as erythrocytosis, heart failure, or cor pulmonale, supplemental oxygen is reasonable if the Po_2 is 59 mm Hg (7.8 kPa) or less or the oxygen saturation is 89% or less. This patient does not meet criteria for supplemental oxygen.

KEY POINTS

- Pulmonary rehabilitation has numerous benefits in patients with COPD, including reduced symptoms, improved quality of life, and decreased frequency of hospitalizations.
- Addition of pulmonary rehabilitation should be considered for patients with COPD and moderate to severe symptoms and patients experiencing at least one exacerbation per year, particularly in those recently hospitalized after an exacerbation.

Bibliography

Labaki WW, Rosenberg SR. Chronic obstructive pulmonary disease. Ann Intern Med. 2020;173:ITC17-ITC32. [PMID: 32745458] doi:10.7326/AITC202008040

Item 64 Answer: C

Educational Objective: Treat an acute COPD exacerbation with glucocorticoids.

The most appropriate treatment is prednisone (**Option C**). The goals of treatment of an acute COPD exacerbation are to relieve acute symptoms and to prevent future exacerbations. If the patient has hypoxia, supplemental oxygen should be used to maintain an oxygen saturation of 88% to 92%. Noninvasive or invasive mechanical ventilation may be necessary if ventilation or oxygenation is inadequate. Acute symptoms should be treated with short-acting β_2-agonists with or without anticholinergic agents. Glucocorticoids are a mainstay of the treatment of COPD exacerbations because they can improve FEV_1 and hypoxia; decrease the need for hospitalization when used early; and decrease the frequency of treatment failures, length of stay, and time to subsequent exacerbations. Short courses of lower-dose oral glucocorticoids (prednisone 40 mg/d for 5 days) have been found to be equivalent to higher doses, longer courses, and intravenous administration.

Supplemental oxygen therapy should be used for patients with acute COPD exacerbations to maintain an oxygen saturation of 88% to 92%. This patient is maintaining oxygen saturation greater than 88% while receiving oxygen through a standard nasal cannula; thus, a high-flow nasal cannula (**Option A**) is unnecessary.

For patients with acute hypercapnic respiratory failure with acidosis due to a COPD exacerbation, noninvasive ventilation with bilevel positive airway pressure (**Option B**) can improve symptoms and reduce intubation rates, length of hospital stay, and mortality. However, this patient has adequate ventilation (as evidenced by her normal pH and P_{CO_2} levels) and does not require noninvasive ventilation.

A sputum culture (**Option D**) is not routinely obtained in patients with a COPD exacerbation because the results rarely affect management.

KEY POINTS

- Glucocorticoids are a mainstay of the treatment of COPD exacerbations because they can improve FEV_1 and hypoxia; decrease the need for hospitalization when used early; and decrease the frequency of treatment failures, length of stay, and time to subsequent exacerbations.
- In patients with COPD exacerbation, short courses of lower-dose oral glucocorticoids (prednisone 40 mg/d for 5 days) have been found to be equivalent to higher doses, longer courses, and intravenous administration.

Bibliography

Dobler CC, Morrow AS, Beuschel B, et al. Pharmacologic therapies in patients with exacerbation of chronic obstructive pulmonary disease: A systematic review with meta-analysis. Ann Intern Med. 2020;172:413-422. [PMID: 32092762] doi:10.7326/M19-3007

H Item 65 Answer: C

Educational Objective: **Treat malignant hyperthermia.**

The most appropriate treatment is dantrolene (**Option C**). This patient has developed malignant hyperthermia after receiving succinylcholine. Malignant hyperthermia is a rare autosomal dominant inherited disorder characterized by diffuse skeletal muscle activation that results from intracellular calcium release. It is triggered most often by inhaled anesthetics and the depolarizing neuromuscular blocker succinylcholine. Presenting signs and symptoms reflect hypermetabolism and include muscle rigidity (including masseter muscle rigidity), tachycardia, tachypnea, laboratory evidence of rhabdomyolysis (elevated serum creatine kinase, potassium, and phosphorus levels and myoglobinuria), and temperature that can be strikingly high, 45.0 °C (113.0 °F) or more. Mortality can reach 10%. Treatment consists of discontinuing the triggering agent, active cooling, and administration of the muscle relaxant dantrolene every 5 to 10 minutes until muscle rigidity and hyperthermia resolve. Dantrolene interferes with intracellular calcium release and is considered an antidote to malignant hyperthermia. Patients should be monitored in the ICU for 24 hours following an episode of malignant hyperthermia.

Acetaminophen (**Option A**) acts as an antipyretic through central nervous system mechanisms. It is ineffective at controlling fever in malignant hyperthermia, which is generated from activation of skeletal muscles.

Cyproheptadine (**Option B**), a serotonin and histamine antagonist, is sometimes used off-label to treat serotonin syndrome. Serotonin syndrome is a less severe hyperthermic reaction triggered by simultaneous use of two or more medications that affect release or reuptake of serotonin. Unlike neuroleptic malignant syndrome, serotonin syndrome usually includes hyperreflexia and myoclonus, does not result in muscle rigidity, and generally resolves spontaneously after 24 hours. Cyproheptadine does not have a role in the treatment of malignant hyperthermia.

The calcium channel blocker diltiazem (**Option D**) blocks calcium influx into vascular and cardiac muscle cells but would not affect the calcium dysregulation of the skeletal muscles that occurs in malignant hyperthermia.

KEY POINTS

- Malignant hyperthermia is a rare cause of severe hyperthermia in response to inhaled anesthetic agents or depolarizing paralytic agents such as succinylcholine, resulting in muscle rigidity, rhabdomyolysis, cardiac arrhythmias, and significant core body temperature elevation.
- Treatment of malignant hyperthermia consists of discontinuing the triggering agent, active cooling, and administration of the muscle relaxant dantrolene.

Bibliography

Hopkins PM, Girard T, Dalay S, et al. Malignant hyperthermia 2020: guideline from the Association of Anaesthetists. Anaesthesia. 2021;76:655-664. [PMID: 33399225] doi:10.1111/anae.15317

Item 66 Answer: A

Educational Objective: **Diagnose central sleep apnea.**

The most likely diagnosis is central sleep apnea (CSA) (**Option A**). The clinical history, risk factors in the form of medical comorbidities, and respiratory tracing from the polysomnogram are most compatible with CSA. CSA is defined by pauses in breathing due to a loss of output from the central respiratory generators in the brainstem to the muscles that make up the respiratory pump. CSA is typically associated with comorbid conditions, most commonly heart failure. Other risk factors include atrial fibrillation and opioid use. The respiratory tracing from the polysomnogram shows the classic configuration of Cheyne-Stokes breathing in CSA, with a crescendo-decrescendo pattern of airflow and intervening breathing pauses as blood carbon dioxide tension falls and the stimulus to breathe dissipates.

Although obstructive sleep apnea (OSA) (**Option B**) can coexist with CSA, this patient lacks some important risk factors (obesity and a thick neck). Respiratory flow in OSA would demonstrate cessation of airflow rather than the waxing and waning of ventilation seen here. In OSA, the full polysomnogram tracing would show continued respiratory effort of the rib cage and abdomen despite lack of airflow. This patient's presentation is more consistent with CSA.

Sleep-related hypoventilation (**Option C**) syndromes are associated with advanced COPD, obesity, restrictive lung diseases related to kyphoscoliosis or neuromuscular disorders, and other diseases. Sustained reductions in oxyhemoglobin saturation (<90% for at least 5 minutes or >30% total sleep time by oximetry or polysomnography) in the setting of a compatible medical condition signify a hypoventilation syndrome. OSA may or may not be an associated feature. The patient's clinical picture and Cheyne-Stokes respiratory tracing are not consistent with sleep-related hypoventilation syndrome.

Approximately 10% of OSA patients treated with positive airway pressure (PAP) exhibit "treatment-emergent CSA" (**Option D**), the significance of which is a matter of debate. In many patients, the central apneas dissipate as patients acclimate to PAP therapy. This patient has no evidence of OSA and is not receiving treatment with PAP, making this an untenable diagnosis.

KEY POINTS

- Central sleep apnea is defined by pauses in breathing due to a loss of output from the central respiratory generators in the brainstem to the muscles that make up the respiratory pump.
- Central sleep apnea is most commonly associated with heart failure, atrial fibrillation, and opioid use.

Bibliography

Costanzo MR. Central sleep apnea in patients with heart failure-how to screen, how to treat. Curr Heart Fail Rep. 2020;17:277-287. [PMID: 32803641] doi:10.1007/s11897-020-00472-0

Item 67 Answer: A

Educational Objective: Treat acute exacerbation of COPD with bilevel positive airway pressure ventilation.

The most appropriate treatment is a trial of noninvasive bilevel positive airway pressure (BPAP) (**Option A**). The patient has acute hypercapnic respiratory failure due to an exacerbation of COPD. Patients who develop acute respiratory acidosis are the subgroup most likely to benefit from an initial trial of BPAP. BPAP delivers a higher level of positive airway pressure during inspiration than during expiration. Tidal volume is proportional with the difference between the inspiratory and expiratory pressures. BPAP offloads the respiratory muscles and augments minute ventilation by helping the respiratory muscle generate an adequate tidal volume. Although she may eventually require mechanical ventilation, BPAP is the first intervention because in patients with COPD it reduces work of breathing, need for intubation, hospital length of stay, and mortality.

Continuous positive airway pressure (CPAP) (**Option B**) delivers a constant airway pressure during inspiration and expiration. No additional pressure above the level of CPAP is provided, and therefore tidal volume is not augmented. Patients must initiate every breath. Although CPAP can be used in patients with hypercapnic respiratory failure due to pulmonary edema or obstructive sleep apnea, in patients with COPD, BPAP has the strongest evidence supporting improved patient outcomes.

The patient has respiratory acidosis; thus strategies to augment tidal volume and support work of breathing are needed. High-flow nasal cannula (**Option C**) allows a decrease in the work of breathing and in dead space; however, it does not augment tidal volumes. This modality has not been studied in severe hypercapnia from acute exacerbations of COPD.

Patients with acute exacerbation of COPD who do not have contraindications to BPAP should have a time-limited trial (<2 hours) to assess whether clinical response has occurred. The rationale is that if the patient responds, outcomes are better. If there is no improvement, intubation and mechanical ventilation (**Option D**) should be instituted because delays are associated with increased mortality.

KEY POINTS

- Patients with COPD who develop acute respiratory acidosis are the subgroup most likely to benefit from an initial trial of noninvasive bilevel positive airway pressure.
- In patients with acute hypercapnic respiratory failure due to COPD, noninvasive bilevel positive airway pressure reduces work of breathing, need for intubation, hospital length of stay, and mortality.

Bibliography

Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50. [PMID: 28860265] doi:10.1183/13993003.02426-2016

Item 68 Answer: A

Educational Objective: Manage newly recognized sepsis with the hour-1 care bundle.

The most appropriate management for this patient is to start antibiotic therapy (**Option A**). The patient may have sepsis

H CONT.

based on tachycardia, fever, and hypotension in the setting of a known or suspected infection. The diagnosis of septic shock may be confirmed by the results of laboratory studies and response to fluid resuscitation. In 2018 the Surviving Sepsis Campaign published revised guidelines suggesting that physicians administer specific bundled care to patients within 1 hour of sepsis recognition. The hour-1 bundle includes initiating fluid resuscitation, obtaining blood cultures, checking serum lactate level, and administering appropriate antibiotics. In this patient, fluid resuscitation has been initiated, blood cultures have been obtained, and serum lactate level is pending; the only other item in the bundle that needs to be addressed is the immediate administration of appropriate antibiotics.

Chest radiography (**Option B**) is often indicated to identify the source of sepsis. This patient has rhonchi on examination, raising the possibility that pneumonia is the source of infection. However, obtaining a chest radiograph should not take priority over administering empiric antibiotics in this patient with presumed sepsis, because delays in administration reduce patient survival.

Indications for intubation (**Option C**) include significant hypoxia, inability to ventilate properly, and airway compromise. Although this patient's respiration rate is elevated, he is not hypoxic and he has no indication of impending airway compromise or ventilatory failure. Therefore, intubation is not indicated.

In patients with suspected sepsis and hypotension, early resuscitation with 30 mL/kg of crystalloid solution is indicated and should be performed as part of the hour-1 bundle. Vasopressor support is indicated if hypotension or organ perfusion persists following adequate fluid resuscitation. Norepinephrine (**Option D**) is the preferred vasopressor because of its ability to improve both vascular tone and myocardial performance without significantly increasing the risk of arrhythmias. In this patient, response to crystalloid resuscitation should be assessed before vasopressor support is provided.

KEY POINTS

- Initiating fluid resuscitation, obtaining blood cultures, checking serum lactate level, and administering appropriate antibiotics is recommended within 1 hour of sepsis recognition.
- In patients with sepsis, delays in administration of empiric antibiotics are associated with reduced patient survival.

Bibliography

Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update [Editorial]. Intensive Care Med. 2018;44:925-928. [PMID: 29675566] doi:10.1007/s00134-018-5085-0

Item 69 Answer: C

Educational Objective: **Screen for lung cancer in a patient at high risk.**

The most appropriate lung cancer screening test to perform is low-dose chest CT (LDCT) (**Option C**). Prevention of lung cancer through reduction in smoking is the most important way to reduce the burden of disease. Survival rates are directly linked to cancer stage at the time of diagnosis. Many lung cancers are diagnosed at a late stage; thus, several randomized clinical trials have evaluated screening measures. The randomized National Lung Screening Trial (NLST) compared LDCT screening with chest radiography over 3 years among patients ages 55 to 74 years with at least a 30-pack-year history of smoking who currently smoked or had quit in the past 15 years. The trial showed a relative mortality reduction of 20% in the LDCT screening group. The U.S. Preventive Services Task Force (USPSTF) and other societies now recommend LDCT screening for lung cancer in high-risk populations. The USPSTF recommends screening patients ages 50 through 80 years who have no symptoms of lung cancer, have at least a 20-pack-year smoking history, and are current smokers or have quit within the last 15 years. Cessation of screening should also be considered in those who have not smoked in 15 years, those with limited life expectancy, and those who would not be candidates for or would not be willing to undergo surgery. This patient is at high risk because of her age and smoking history and should undergo annual LDCT. Screening has potential harms, including the consequences of evaluating abnormal results (additional tests and procedures), radiation exposure, patient distress, and overdiagnosis. It is desirable that lung cancer screening take place in a center that has radiologic, diagnostic, and treatment capabilities similar to those of centers involved in the NLST.

Chest radiography (**Option A**) and sputum cytology (**Option D**) are not recommended for lung cancer screening. Several clinical trials have found no mortality benefit to screening with either method.

Fluorodeoxyglucose PET (**Option B**) plays a role in evaluating patients once a pulmonary nodule or mass is identified on CT. It does not have a role in routine lung cancer screening.

There is moderate certainty that annual screening for lung cancer with LDCT is of net benefit in asymptomatic persons who are at high risk for lung cancer. This patient fulfills all the criteria for benefiting from LDCT lung cancer screening. Not offering LDCT lung cancer screening (**Option E**) may result in unnecessary early mortality.

KEY POINTS

- Annual lung cancer screening should be performed in patients aged 50 through 80 years who have no symptoms of lung cancer, have at least a 20-pack-year smoking history, and are current smokers or have quit within the last 15 years.
- Cessation of lung cancer screening should be considered in those who have not smoked in 15 years, those with limited life expectancy, and those who would not be candidates for or would not be willing to undergo surgery.

Bibliography

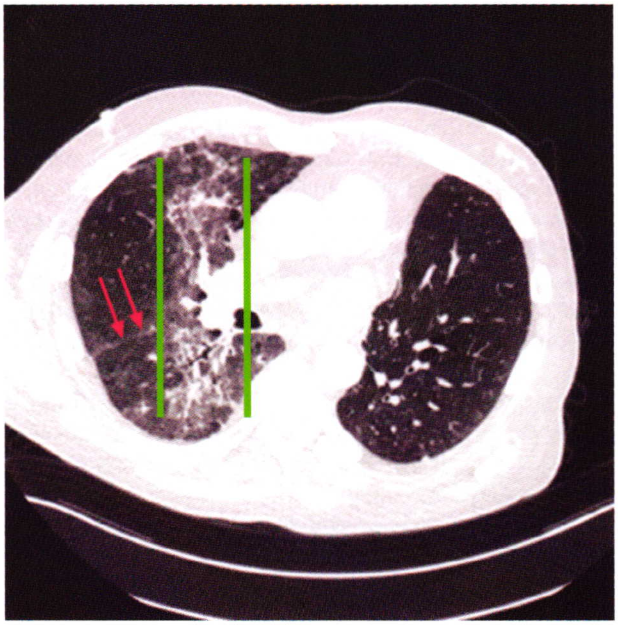
Mazzone PJ, Silvestri GA, Patel S, et al. Screening for lung cancer: CHEST guideline and expert panel report. Chest. 2018;153:954-985. [PMID: 29374513] doi:10.1016/j.chest.2018.01.016

H

Item 70 Answer: D

Educational Objective: Diagnose radiation pneumonitis.

The most likely diagnosis, based on the patient's clinical and radiologic picture, is radiation pneumonitis (**Option D**). Typically developing 4 to 12 weeks after completion of radiotherapy, the lung opacities can cross multiple lobes (as shown; red arrows point to the major fissure separating the right middle and lower lobes) and appear delineated by "straight lines" corresponding to the radiation field (as shown, bordered by green lines).



The classic symptoms are dyspnea on exertion, nonproductive cough, and hypoxemia; low-grade fevers are also common. A subset of patients develop radiation fibrosis 6 to 12 months after treatment. Immune checkpoint inhibitors such as pembroluzimab are immunomodulatory drugs that are widely used in the management of advanced malignancies, including non–small cell lung cancer. Although they have significant clinical benefits, these drugs are also associated with significant adverse effects, including pneumonitis. In contrast to radiation pneumonitis, immune checkpoint inhibitor–related pneumonitis usually does not cross lung fissures. Pulmonary toxicity of immune checkpoint inhibitors may also manifest as radiation recall pneumonitis, a variant of radiation pneumonitis, which manifests in areas of previous radiation exposure. Radiation recall pneumonitis can occur with multiple other chemotherapeutic agents, even years after radiation therapy.

Hospital-acquired pneumonia (**Option A**) is an important consideration in any immune-compromised patient with new symptoms and radiographic infiltrates. In this patient, however, the absence of any identifiable pathogen on bronchoalveolar lavage cultures as well as localization of infiltrates to the radiation field rule out this diagnosis.

Hypersensitivity pneumonitis (HP) (**Option B**) results from exposure to a wide variety of antigens that provoke an exaggerated immune response in susceptible persons. High-resolution CT scan will show micronodules and ground-glass opacities. However, the absence of a discrete exposure and radiologic findings confined to the previous radiation field do not fit the clinical picture of HP.

There is no clinical suggestion of volume overload in this patient; hence, pulmonary edema (**Option C**) is not the likely cause. In addition, pulmonary edema typically results in bilateral symmetric radiographic infiltrates.

KEY POINTS

- Patients with radiation pneumonitis typically develop cough, shortness of breath, and radiographic infiltrates 4 to 12 weeks after radiation exposure.
- Pulmonary toxicity of immune checkpoint inhibitors may also manifest as radiation recall pneumonitis, a variant of radiation pneumonitis, in areas of previous radiation exposure.

Bibliography

Jain V, Berman AT. Radiation pneumonitis: old problem, new tricks. Cancers (Basel). 2018;10. [PMID: 29970850] doi:10.3390/cancers10070222

Item 71 Answer: A

H

Educational Objective: Evaluate a pleural effusion in the ICU.

The most appropriate diagnostic test to perform is bedside thoracic ultrasonography (**Option A**). The patient is presenting with septic shock and hypoxemic respiratory failure. Her presentation is secondary to a multifocal pneumonia with an associated left pleural effusion. Once a pleural effusion is detected on chest radiograph, bedside thoracic ultrasonography can be used to characterize the fluid and the feasibility of drainage. Thoracic point-of-care ultrasonography is a helpful addition particularly in patients who are semirecumbent, such as those who are critically ill, and does not necessitate transporting the patient from the ICU or interrupting resuscitation. Thoracic ultrasonography allows for the easy identification of a free-flowing or loculated pleural effusion and can differentiate between solid masses and loculated effusions. The presence of a loculated pleural effusion in the setting of severe community-acquired pneumonia would be an indication for diagnostic sampling and drainage of the effusion.

Advantages of CT imaging with contrast (**Option B**) include the ability to detect small amounts of pleural fluid; assessment of coexisting intrathoracic abnormalities such as pulmonary masses and malignant pleural disease; and identification of an empyema, as enhancement of the pleura around the fluid creates a lenticular-shaped opacity.

CONT.

However, CT imaging requires the patient to be removed from the ICU and exposes the patient to irradiation.

A lateral decubitus film (**Option C**) would also differentiate between a free-flowing and a loculated pleural effusion. However, it is now rarely used in the ICU because bedside ultrasonography is easy to access and to use. In addition, a lateral decubitus film would not demonstrate the feasibility of drainage as ultrasound does.

Finally, a thoracic MRI (**Option D**) can effectively display pleural tumors, chest wall invasion, spinal cord invasion, and pleural effusions. However, it is not as useful as thoracic ultrasonography and CT for evaluation of parapneumonic effusions, it is expensive, and it requires the patient to be moved from the ICU.

KEY POINTS

- Thoracic ultrasonography allows for the easy identification of a free-flowing or loculated pleural effusion and can differentiate between solid masses and loculated effusions.
- Thoracic point-of-care ultrasonography is a helpful addition particularly in patients who are semirecumbent, such as those who are critically ill, and does not necessitate moving the patient from the ICU.

Bibliography

Porcel JM. Chest imaging for the diagnosis of complicated parapneumonic effusions. Curr Opin Pulm Med. 2018;24:398-402. [PMID: 29517587] doi:10.1097/MCP.0000000000000485

Item 72 Answer: D

Educational Objective: Evaluate shock with transthoracic echocardiography.

The most appropriate management is transthoracic echocardiography (**Option D**). This patient has features consistent with cardiogenic shock (cool extremities, pulmonary crackles, jugular venous distention, altered mental status, oliguria). Cardiogenic shock occurs when a primary cardiac insult causes decreased cardiac output. In addition to a physical examination, the American Heart Association (AHA) recommends laboratory testing for myocardial ischemia and heart failure, chest radiography, electrocardiography, and transthoracic echocardiography. A transthoracic echocardiogram provides information on heart size, systolic and diastolic function, regional wall motion abnormalities, and valvular disease. Regional wall motion abnormalities suggest coronary artery disease, and changes in the myocardium can suggest conditions such as cardiac amyloid. Echocardiography may also provide prognostic information.

In the absence of contraindications, additional imaging with CT angiography (**Option A**) is appropriate if pulmonary embolism is considered high probability. CT angiography has significantly improved the accuracy of evaluating pulmonary embolism and could be considered in this patient if the initial tests do not support myocardial infarction or other cardiac causes of this patient's shock. However, CT angiography would not be part of the initial battery of tests, and transporting this unstable patient would pose additional risk.

Pulmonary artery catheters (**Option B**) have lost favorability in recent years because several large studies and meta-analyses suggest no benefit to patients, and in some cases suggest increased risk, when they are used to guide therapy. The use of a pulmonary artery catheter for hemodynamic monitoring may be reasonable when the diagnosis remains uncertain or the patient has not responded to resuscitation efforts.

The AHA recommends transthoracic echocardiography as the initial noninvasive imaging test following a chest radiograph. If the transthoracic echocardiogram fails to provide adequate images or the diagnosis remains uncertain, the AHA recommends considering transesophageal echocardiography (**Option C**).

KEY POINT

- The initial evaluation of cardiogenic shock includes laboratory testing for myocardial ischemia and heart failure, chest radiography, electrocardiography, and transthoracic echocardiography.

Bibliography

van Diepen S, Katz JN, Albert NM, et al; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: A scientific statement from the American Heart Association. Circulation. 2017;136:e232-e268. [PMID: 28923988] doi:10.1161/CIR.0000000000000525

Item 73 Answer: D

Educational Objective: Prevent malnutrition in a critically ill patient.

The most appropriate management is to stop enteral nutrition and start parenteral nutrition (**Option D**). Malnutrition in critically ill patients leads to increased morbidity and mortality. All patients admitted to the ICU should have a nutritional evaluation. Enteral nutrition should start within 24 to 48 hours of admission in critically ill patients. Guidelines recommend that parenteral nutrition to achieve full nutritional goals should be started only after 7 to 10 days of inability to achieve more than 60% of energy and protein requirements by the enteral route alone. Initiating parenteral nutrition before 7 to 10 days in critically ill patients on some enteral nutrition does not improve outcomes and may be detrimental to the patient.

Megestrol acetate (**Option A**) is an appetite stimulant that has been used in patients with cancer-related anorexia-cachexia and in older adults with failure to thrive. This patient's inability to meet her caloric needs is related to intolerance of enteral feedings as evidenced by bloating and emesis, not anorexia.

Methylnaltrexone (**Option B**) is indicated to manage constipation related to opiates. Although the patient uses

H CONT.

opiates, the presence of liquid feces in the ostomy bag and the presence of bowel sounds argue against constipation as a cause of intolerance.

In critically ill patients, increasing fiber in the enteral diet (**Option C**) can decrease diarrhea and improve tolerance to enteral nutrition. However, bloating and emesis are the result of her intolerance to enteral feeding. In addition, a more urgent need now is the provision of adequate nutrition.

KEY POINTS

- Enteral nutrition should start within 24 to 48 hours of admission in critically ill patients.
- In critically ill patients, supplemental parenteral nutrition should be started after 7 to 10 days of inability to achieve more than 60% of energy and protein requirements by the enteral route alone.

Bibliography

McClave SA, Taylor BE, Martindale RG, et al; Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40:159-211. [PMID: 26773077] doi:10.1177/0148607115621863

Item 74 Answer: D

Educational Objective: Treat opioid-related sleep apnea.

The most appropriate treatment is a pain rehabilitation program (**Option D**). A sleep study showed that this patient has central sleep apnea (CSA). CSA is defined by pauses in airflow due to loss of output from the central respiratory generators in the brainstem to the respiratory muscles, resulting in lack of respiratory effort. There are few clinical trials proving a role for specific treatment of CSA, so initial management should target modifiable risk factors. For example, reduction or elimination of opioids improves CSA. Medical optimization of heart failure (with drugs or devices, optimizing fluid balance in the setting of volume overload, or surgery such as valve repair or cardiac transplantation) has been shown to improve CSA. This patient's CSA is most likely related to use of opioid analgesics. Because initial management of CSA should target modifiable risk factors, a pain rehabilitation program to help the patient curtail opioid use is appropriate. Additionally, a more appropriate long-term pain management strategy is needed to improve her quality of life. However, adherence to a pain management plan that includes opioid reduction may be difficult and failure is frequent.

Adaptive servo-ventilation (ASV) (**Option A**) is a form of positive airway pressure therapy that effectively suppresses CSA. Small observational studies suggest that it has some efficacy in opioid-induced CSA, but controlled trials are lacking to demonstrate improvements in important outcomes. Although a trial of ASV may be warranted in some patients with opioid-related CSA, it should be preceded by an attempt to reduce opioid use and to try other treatments with proven efficacy and safety. Consideration should also be given to an increased risk of death associated with ASV treatment in a large trial of patients with heart failure defined by a left ventricular ejection fraction less than 45%.

Continuous positive airway pressure (CPAP) (**Option B**) is effective at maintaining upper airway patency in obstructive sleep apnea (OSA) but is generally ineffective in treating CSA, a disorder of ventilatory control. In fact, when CPAP is used in the treatment of obstructive sleep apnea, it can occasionally result in CSA (a condition called treatment-emergent central sleep apnea). CPAP may be appropriate in some patients with combined CSA and OSA, as determined by polysomnography.

The patient has nonspecific fatigue and tiredness. Modafinil (**Option C**) is used to combat excessive sleepiness associated with hypersomnia syndromes, such as narcolepsy, and residual sleepiness associated with OSA despite adequate CPAP therapy. A stimulant medication is not indicated for this patient.

KEY POINT

- The initial management of central sleep apnea should target modifiable risk factors such as the reduction or elimination of opioids or medical optimization of heart failure.

Bibliography

Wasef S, Mir S, Ryan C, et al. Treatment for patients with sleep apnea on opioids for chronic pain: results of the OpSafe trial. J Clin Sleep Med. 2021;17:819-824. [PMID: 33382032] doi:10.5664/jcsm.9064

Item 75 Answer: D

Educational Objective: Treat an acute COPD exacerbation with azithromycin.

The most appropriate additional treatment is oral azithromycin (**Option D**). Infectious agents in COPD exacerbations are often viral but can be bacterial. The most common bacterial causes include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae*. Antibiotics are indicated in patients who have increased sputum purulence and either increased dyspnea or increased sputum volume, as well as in patients who require invasive or noninvasive mechanical ventilation. The recommended duration of antibiotic therapy is 5 days. The antibiotic used should be based on local bacterial resistance patterns; common initial treatments include amoxicillin with clavulanic acid and macrolide and tetracycline antibiotics. Thus, azithromycin would be an appropriate treatment for this patient.

The methylxanthines (aminophylline and theophylline) are now rarely used to treat COPD. Theophylline (**Option A**) has been shown to improve functional capacity and reduce the number of exacerbations. However, it has a narrow window between therapeutic and toxic dosages and therefore is used only for patients with advanced COPD who have refractory symptoms not controlled using standard therapy. Studies of the use of either aminophylline or theophylline during acute exacerbations have shown no benefit.

This patient does not have a fever or an infiltrate on chest radiograph; thus, broad-spectrum antibiotics such as piperacillin-tazobactam (**Option B**) would be inappropriate. Potential indications for *Pseudomonas* coverage with piperacillin-tazobactam would include chronic colonization with *Pseudomonas* or previous documented infection within the previous 12 months, very severe COPD, bronchiectasis on imaging, broad-spectrum antibiotic use in the previous 3 months, or chronic oral glucocorticoid use.

For patients with acute hypercapnic respiratory failure with acidosis due to a COPD exacerbation, noninvasive ventilation with bilevel positive airway pressure (**Option C**) can improve symptoms and reduce intubation rates, length of hospital stay, and mortality. However, this patient has adequate ventilation (as evidenced by his normal pH and Pco_2 levels) and does not require noninvasive ventilation.

KEY POINTS

- Antibiotics are indicated in patients with COPD exacerbation who have increased sputum purulence and either increased dyspnea or increased sputum volume, as well as in patients who require invasive or noninvasive mechanical ventilation.
- Commonly used antibiotics for COPD exacerbations include amoxicillin with clavulanic acid and macrolide and tetracycline antibiotics.

Bibliography

Dobler CC, Morrow AS, Beuschel B, et al. Pharmacologic therapies in patients with exacerbation of chronic obstructive pulmonary disease: A systematic review with meta-analysis. Ann Intern Med. 2020;172:413-422. [PMID: 32092762] doi:10.7326/M19-3007

Item 76 Answer: A

Educational Objective: Diagnose excessive laboratory testing as the cause of anemia.

The most appropriate strategy is discontinuation of routine blood testing (**Option A**). Numerous studies in the literature have documented excessive use of laboratory studies in the hospital setting in general and in the ICU in particular. Estimates suggest that approximately 20% of laboratory tests obtained in hospitalized patients are not needed, resulting in waste. In addition to the financial impact to the health care system, overutilization invariably results in false-positive test results, leading to further downstream testing. Studies show that excessive blood draws can result in iatrogenic anemia, as is likely the case in this patient. Efforts to reduce unnecessary laboratory testing have the dual benefit of improving patient safety and reducing health care expenditures. Studies have shown that a reduction in laboratory testing does not lead to adverse patient outcomes, and some studies suggest a decrease in hospital lengths of hospital stay and the need for transfusion. The first management step in this patient is to discontinue daily routine laboratory testing. Laboratory testing should only be undertaken in response to specific clinical questions.

Erythropoietin-stimulating agents (**Option B**) and iron supplementation are used in protocols for patients who cannot receive blood. In this patient, reducing blood loss through discontinuation of routine daily blood tests is a much more practical, safe, and economical management approach for anemia.

Anemia in nonbleeding critically ill patients can be challenging to evaluate because the inflammatory state may result in inflammatory anemia. Iron studies (**Option C**) can help diagnose inflammatory anemia. However, inflammatory anemia usually does not result in hemoglobin concentrations of less than 10 g/dL (100 g/L) and certainly not over 12 days, and since hemolysis has been excluded, the elevated reticulocyte count suggests blood loss.

Guidelines recommend transfusion of erythrocytes (**Option D**) in nonbleeding critically ill patients at a hemoglobin threshold of 7 g/dL (70 g/L). In patients with acute coronary syndrome, the threshold is unclear, but guidelines recommend thresholds of 8 to 9 g/dL (80-90 g/L). This patient does not require a transfusion but rather discontinuation of routine daily blood tests.

KEY POINTS

- Approximately 20% of laboratory tests obtained in hospitalized patients are not needed.
- Excessive laboratory testing in hospitalized patients can result in iatrogenic anemia.

Bibliography

Bindraban RS, Ten Berg MJ, Naaktgeboren CA, et al. Reducing test utilization in hospital settings: A narrative review. Ann Lab Med. 2018;38:402-412. [PMID: 29797809] doi:10.3343/alm.2018.38.5.402

Item 77 Answer: A

Educational Objective: Treat preeclampsia with delivery.

The most appropriate next step in management for this patient with preeclampsia is delivery (**Option A**). Preeclampsia is a disorder of pregnancy that is associated with new-onset hypertension, most often occurring after 20 weeks of gestation. Although hypertension is often accompanied by new-onset proteinuria, some women present with hypertension and signs or symptoms of end-organ dysfunction without proteinuria. The presence of one or more of the following findings of end-organ dysfunction indicates a diagnosis of preeclampsia with severe features: thrombocytopenia (<100,000/µL [100×10^9/L]); liver enzyme levels twice the upper limit of normal; severe persistent right upper quadrant or epigastric pain not accounted for by alternative diagnoses; kidney injury (serum creatinine concentration >1.1 mg/dL [97.2 µmol/L] or a doubling of the serum creatinine concentration in the absence of another kidney disease); pulmonary edema; or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbance. Patients with preeclampsia are also at risk of developing HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count),

H CONT.

which has been associated with increased rates of maternal morbidity and mortality. Definitive treatment of severe preeclampsia in patients who are at or beyond 34 weeks' gestation includes emergent management of severe hypertension and prompt delivery.

Antenatal glucocorticoids (betamethasone or dexamethasone) (**Option B**) to promote fetal lung maturity should be administered before 34 weeks of gestation for a patient with nonsevere preeclampsia in whom delivery in the next 7 days is anticipated. Delivery should not be delayed for the administration of glucocorticoids in the late preterm period.

Angiotensin-converting enzyme inhibitors, including enalapril (**Option C**), are teratogenic and should be avoided during pregnancy. Recommended first-line antihypertensives for urgent blood pressure control in pregnancy include intravenous labetalol, intravenous hydralazine, and immediate-release nifedipine.

Intravenous sodium nitroprusside (**Option D**) is recommended only for hypertensive emergencies resistant to first-line therapy and the presence of end-organ damage. When used, it should be infused for the shortest amount of time possible because of cyanide and thiocyanate toxicity risk in the patient and fetus or newborn. Sodium nitroprusside can also be associated with increased intracranial pressure with potential worsening of cerebral edema in the patient.

KEY POINT

- In patients who are at or beyond 34 weeks' gestation and who develop preeclampsia with severe features, emergent management of severe hypertension and prompt delivery are recommended to avoid maternal and fetal complications.

Bibliography

Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. Obstet Gynecol. 2020;135:e237-e260. [PMID: 32443079] doi:10.1097/AOG.0000000000003891

H

Item 78 Answer: B

Educational Objective: Diagnose pulmonary hypertension.

The most appropriate next step for this patient is right heart catheterization (**Option B**). This patient has symptoms (progressive dyspnea) and signs (elevated central venous pressure, venous *a* wave, fixed splitting of S_2, tricuspid regurgitation) of pulmonary hypertension (PH). If PH is suspected, transthoracic echocardiography can estimate pulmonary artery systolic pressure. However, echocardiography does not confirm the diagnosis of PH because pressure estimation by echocardiography may be inaccurate. Right heart catheterization confirms the diagnosis of PH and is an essential component of the diagnostic evaluation. Guidelines recommend referral of patients with severe pulmonary hypertension or right ventricular dysfunction to a pulmonary hypertension referral center. Data suggest that patients who are evaluated for pulmonary hypertension outside of pulmonary hypertension referral centers receive an incorrect diagnosis as much as 33% of the time. The evaluation of PH also includes additional testing to identify an underlying cause of PH such as lung disease, left-sided heart failure, chronic thromboembolic pulmonary hypertension, and causes of nocturnal hypoxemia.

Coronary angiography (**Option A**) might be considered if ischemic cardiomyopathy with left ventricular failure is suspected as the cause of PH. However, this patient has no symptoms or ECG or echocardiographic findings to support this diagnosis. Coronary angiography is not indicated.

The current classification system subdivides PH into five groups, which are based on similarities in mechanisms, hemodynamics, clinical presentation, and approach to treatment. Group 1 includes patients with pulmonary arterial hypertension (PAH), including those with idiopathic and heritable disease, and disease related to drugs and toxins, connective tissue diseases, HIV infection, schistosomiasis, congenital heart disease, and portal hypertension. High-dose calcium channel blockers, such as nifedipine (**Option C**), can be effective treatment in a small number of group 1 patients who are "vasoreactive" by demonstrating marked improvement in mean pulmonary artery pressure with administration of nitric oxide, epoprostenol, or adenosine during right heart catheterization. Sildenafil (**Option D**), a phosphodiesterase-5 inhibitor, may be effective in mild to moderate PAH in the absence of vasoreactivity. However, neither nifedipine nor sildenafil is indicated for the treatment of PAH until the diagnosis of PH has been confirmed and other causes of PH have been excluded.

KEY POINTS

- Pulmonary hypertension should be suspected in patients with progressive dyspnea, elevated central venous pressure, prominent venous *a* wave, fixed splitting of S_2, and the murmur of tricuspid regurgitation.
- Right heart catheterization and measurement of pulmonary artery pressure is the diagnostic gold standard for pulmonary hypertension.

Bibliography

Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report. Chest. 2019;155:565-586. [PMID: 30660783] doi:10.1016/j.chest.2018.11.030

Item 79 Answer: A

H

Educational Objective: Treat severe hypothermia with active internal rewarming.

The most appropriate treatment is active internal rewarming (**Option A**). This patient has severe hypothermia, defined by a core temperature of less than 28.0 °C (82.4 °F) in the setting of ongoing coma or cardiovascular collapse. Other findings in severe hyperthermia are absent reflexes, ventricular arrhythmia, asystole, and apnea. If a severely hypothermic patient becomes pulseless and requires resuscitation, it is reasonable to continue cardiopulmonary resuscitation for a prolonged period until the patient can be rewarmed. Methods of internal rewarming include infusion of heated intravenous crystalloid solution as well as lavage of the peritoneal or pleural cavities with warm fluids. During active rewarming, core temperature should be monitored with an esophageal temperature probe, as rectal and bladder temperatures will lag behind the rising core temperature during the rewarming process.

Extracorporeal support, including cardiopulmonary bypass (**Option B**), is recommended for severely hypothermic patients in cardiac arrest because it maximizes the rewarming rate and can provide hemodynamic support.

Hemodialysis (**Option C**) can be used for warming, depending on the clinical circumstances. Acid-base and electrolyte abnormalities are common in hypothermia. These values, along with markers of coagulopathy, will improve with rewarming but should be serially measured. The patient has metabolic acidosis and hyperkalemia, but neither is severe enough to warrant hemodialysis, and rewarming can be accomplished by other means.

Hypothermic patients who are shivering will passively rewarm themselves (**Option D**) if they are removed from the cold environment and given adequate insulation to prevent heat loss, but as hypothermia progresses, shivering stops. For core temperatures of 28.0 °C to 35.0 °C (82.4 °F to 95.0 °F), active external warming is usually sufficient. This consists of warming blankets and forced warm air. For temperatures less than 28.0 °C (82.4 °F) and for patients who fail to respond adequately to active external rewarming, active internal rewarming methods should be applied.

KEY POINTS

- Severe hypothermia is defined by a core temperature of less than 28.0 °C (82.4 °F) in the setting of ongoing coma or cardiovascular collapse.
- For temperatures less than 28.0 °C (82.4 °F) and for patients who fail to respond adequately to active external rewarming, active internal rewarming methods, including infusion of heated intravenous crystalloid solution and lavage of the peritoneal or pleural cavities with warm fluids, should be applied.

Bibliography

Paal P, Brugger H, Strapazzon G. Accidental hypothermia. Handb Clin Neurol. 2018;157:547-563. [PMID: 30459025] doi:10.1016/B978-0-444-64074-1.00033-1

Item 80 Answer: A

Educational Objective: Treat gastroesophageal reflux disease in a patient with asthma.

The most appropriate management for this patient is to begin omeprazole (**Option A**). The patient has a normal Asthma Control Test score, normal spirometry, and normal fractional exhaled nitric oxide, which all confirm that his asthma is well controlled. Measurement of the fraction of nitric oxide in an exhaled breath sample provides a noninvasive way to quantify eosinophilic airway inflammation and serves as a complementary tool in the diagnosis and management of asthma. However, his cough and other symptoms suggest gastroesophageal reflux disease (GERD), a common asthma comorbidity. At each asthma visit, clinicians should assess patient symptom control, inhaler technique and adherence, and comorbidities such as rhinosinusitis, obesity, and GERD. GERD is more common in patients with asthma than the general population and may contribute to respiratory symptoms such as cough, wheezing, and dyspnea. Potential mechanisms by which GERD may cause cough or worsened asthma control include increased vagal tone, bronchial hyperreactivity, and microaspiration of gastric contents into the upper airways. Empiric treatment of GERD in patients without worrisome symptoms such as weight loss, dysphagia, or hematemesis consists of a proton pump inhibitor such as omeprazole.

Switching to a medium-dose inhaled glucocorticoid (**Option B**) is not needed because the patient is tolerating the current therapy and it is controlling his asthma symptoms.

Stepping up this patient's therapy by increasing the strength of his inhaled glucocorticoid (**Option C**) maintenance inhaler is not necessary without signs of worsening asthma.

Performing upper endoscopy (**Option D**) is unnecessary in patients with uncomplicated GERD without suspicion for malignancy, erosive esophagitis, or mechanical issues causing dysphagia, such as webs, rings, or strictures. Patients whose reflux symptoms do not improve should be considered for further testing such as endoscopy and 24-hour esophageal pH monitoring.

KEY POINTS

- Gastrointestinal reflux disease is more common in patients with asthma than the general population and may contribute to respiratory symptoms such as cough, wheezing, and dyspnea.
- Patients with respiratory symptoms and gastroesophageal reflux disease should be treated with an empiric trial of a proton pump inhibitor.

Bibliography

Vaezi MF, Katzka D, Zerbib F. Extraesophageal symptoms and diseases attributed to GERD: where is the pendulum swinging now? Clin Gastroenterol Hepatol. 2018;16:1018-1029. [PMID: 29427733] doi:10.1016/j.cgh.2018.02.001

Item 81 Answer: D

Educational Objective: Diagnose mesothelioma.

The most appropriate diagnostic test is thoracoscopic pleural biopsy (**Option D**). This patient has a unilateral exudative pleural effusion in the setting of pleural thickening and evidence of asbestos exposure. This clinical scenario strongly

H CONT.

suggests malignant pleural mesothelioma. Malignant pleural mesothelioma is a rare neoplasm that originates from the cells that line the pleural cavity (mesothelium). It can present as small nodules, plaque-like masses, or confluent sheets that can encase the lung. It is associated with inhalational exposure to asbestos fibers and has a latency of 20 to 40 years. Tissue biopsy is required to confirm the diagnosis; it can be performed with medical thoracoscopy or video-assisted thoracoscopic surgery, which has 90% sensitivity for malignancy. Because mesothelioma can be difficult to diagnose, patients will typically present with advanced disease. Other conditions that may have a similar presentation include a chronic empyema and malignant conditions such as sarcomas and peripheral adenocarcinomas.

The sensitivity of pleural fluid cytology for the diagnosis of mesothelioma is as low as 5%; therefore a pleural biopsy is required to make the diagnosis. Adding a closed pleural biopsy to thoracentesis increases the sensitivity to approximately 36%. Medical or surgical thoracoscopy has greater than 90% sensitivity for malignancy. Therefore, neither a closed biopsy (**Option A**) nor a repeat thoracentesis (**Option C**) is the most appropriate diagnostic test.

Once the diagnosis is made, fluorodeoxyglucose PET (**Option B**) should be performed to evaluate the extent of the disease and help with staging. PET will not be as useful before biopsy because it will not differentiate between an infectious and an inflammatory cause of the pleural thickening. After tissue confirmation, mesothelioma is staged according to the TNM system; PET is often performed to help determine the extent of involvement. If there is limited involvement and no distant disease, some patients will benefit from surgery as well as chemotherapy and radiation. Prognosis for mesothelioma depends on the histologic features (sarcomatoid versus epithelioid) and staging at diagnosis, but overall it remains poor (median survival, 6-9 months).

KEY POINT

- For suspected mesothelioma, tissue biopsy is required to confirm the diagnosis; biopsy can be performed with medical thoracoscopy or video-assisted thoracoscopic surgery.

Bibliography

Scherpereel A, Opitz I, Berghmans T, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. Eur Respir J. 2020;55. [PMID: 32451346] doi:10.1183/13993003.00953-2019

Item 82 Answer: C

Educational Objective: **Screen a patient with COPD for air travel safety.**

The most appropriate management is resting pulse oximetry (**Option C**). Patients with underlying lung disease are at risk for significant hypoxia during air travel as a result of the decreased oxygen tension of inspired air at higher altitudes. Commercial airlines are required to pressurize cabins to the equivalent of approximately 2500 meters (~8200 feet) in altitude with occasional pressurization to an equivalent altitude of about 3000 meters (~10,000 feet) for short durations, if necessary, to accommodate flying conditions. People with normal cardiopulmonary function experience very little change in oxygenation at these altitudes. In patients whose baseline arterial Po$_2$ is less than 95 mm Hg, however, flying altitudes cause a much greater decrease in oxygen saturation because these patients are on the steep portion of the oxyhemoglobin dissociation curve. A patient whose oxygenation as measured by pulse oximetry (Spo$_2$) is 90% at sea level may only have an Spo$_2$ of 84% at 2500 meters (~8200 feet), which can result in symptoms of hypoxia. Resting pulse oximetry is helpful in screening patients for in-flight hypoxemia. Patients with resting Spo$_2$ greater than 95% are unlikely to experience significant hypoxemia in flight. Patients with resting Spo$_2$ between 92% and 95% require assessment of risk factors and may need additional testing such as high-altitude simulation testing, if available. For those whose resting Spo$_2$ is less than 92%, supplemental oxygen should be prescribed and there is no need for additional testing. Typically, if patients do not require oxygen at baseline, then prescribing 2 L/min of oxygen is sufficient.

High-altitude simulation testing (**Option A**) is considered the gold standard of clinical testing in this scenario. However, it is not widely available and thus is not the first choice for testing.

Patients who require greater than 4 L/ min of oxygen at rest should not travel (**Option B**) because of the uncertain ability to deliver sufficient oxygen during the flight to prevent hypoxemia. However, this patient has not required any oxygen at baseline and should not be disqualified preemptively from flying.

Because this patient is at potential risk for in-flight hypoxemia, no further testing (**Option D**) is not the best management. His assessment should begin with measurement of Spo$_2$.

KEY POINTS

- Resting pulse oximetry is helpful in screening patients for in-flight hypoxemia.
- Patients not using baseline oxygen and with a resting Spo$_2$ less than 92% should be prescribed supplemental oxygen during air travel without additional testing.

Bibliography

Edvardsen A, Akerø A, Christensen CC, et al. Air travel and chronic obstructive pulmonary disease: a new algorithm for pre-flight evaluation. Thorax. 2012;67:964-9. [PMID: 22767877] doi:10.1136/thoraxjnl-2012-201855

Item 83 Answer: A

H

Educational Objective: **Diagnose connective tissue disease–associated interstitial lung disease.**

The most likely diagnosis in this patient is interstitial lung disease (ILD) associated with connective tissue disease (**Option A**). ILD is common among patients with connective tissue disease and can occasionally be the first manifestation. In this patient, systemic sclerosis is suggested by the presence of Raynaud phenomenon, gastroesophageal reflux disease, "puffy fingers" (a finding of early skin disease), and positive antitopoisomerase I (anti-Scl-70) antibody. A patulous esophagus can be seen on the chest CT scan. Radiographic findings mirror those of other idiopathic interstitial pneumonias, with the nonspecific interstitial pneumonia pattern characterized by ground-glass opacities with predominance at the base of the lungs seen in this patient. This radiographic pattern is present in more than 80% of persons with systemic sclerosis–associated ILD. In patients with diffuse parenchymal lung disease, the presence of an underlying connective tissue disease has prognostic and therapeutic implications. In contrast to idiopathic interstitial pneumonia, patients with connective tissue disease–associated ILD are treated with immunomodulatory medications and tend to have a more favorable prognosis.

Hypersensitivity pneumonitis (**Option B**) results from exposure to a wide variety of antigens that provoke an exaggerated immune response in susceptible persons. High-resolution CT imaging of the chest shows findings of ground-glass opacities and centrilobular micronodules that are mid- and upper-lung predominant. However, this patient's chest radiographic findings, lack of environmental exposures, and findings of systemic sclerosis make the diagnosis of hypersensitivity pneumonitis unlikely.

Idiopathic pulmonary fibrosis (IPF) (**Option C**) is the most common idiopathic interstitial pneumonia. It occurs predominantly in older persons; the diagnosis of IPF is rare in those younger than 50 years of age. Gradual onset of dyspnea and cough over months to years is typical.

Sarcoidosis (**Option D**) is a granulomatous disease of unknown cause that can affect multiple organ systems, including the lungs. Frequent radiographic findings of sarcoidosis include lymphadenopathy and the presence of nodules along bronchovascular bundles. This patient's radiographic findings are not consistent with sarcoidosis.

KEY POINTS

- Interstitial lung disease is common among patients with connective tissue disease and can occasionally be the first manifestation.
- Most patients with systemic sclerosis–related lung disease have a nonspecific interstitial pneumonia pattern characterized by ground-glass opacities with predominance at the base of the lungs.

Bibliography

Perelas A, Silver RM, Arrossi AV, et al. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med. 2020;8:304-320. [PMID: 32113575] doi:10.1016/S2213-2600(19)30480-1

Item 84 Answer: A

Educational Objective: Prevent stress ulcers in a critically ill patient.

A strategy of gastric acid suppression with a proton pump inhibitor is most likely to reduce the risk of gastrointestinal bleeding (**Option A**) in this patient. A 2020 systematic review and network meta-analysis of 72 trials involving 12,660 patients found that the benefit of gastric acid suppression to reduce the risk of gastrointestinal bleeding in critically ill patients is finely balanced against harms. There is moderate evidence that compared with placebo, proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), but not sucralfate, reduce the incidence of gastrointestinal bleeding, with PPIs likely to be more effective than H2RAs. Patients at highest risk for gastrointestinal bleeding (risk >4%) benefited the most. Patients at highest risk were identified as those with a coagulopathy, those with chronic liver disease, and those receiving mechanical ventilation but not enteral nutrition. Highest risk patients also included those with two or more of the following risk factors: mechanical ventilation with enteral nutrition, acute kidney injury, sepsis, and shock. Compared with placebo, the absolute difference in bleeding rates for patients at highest risk receiving a PPI was 3.3%. This patient is at high risk for gastrointestinal bleeding and use of a PPI will decrease this risk.

Both PPIs and H2RAs may increase the risk of pneumonia (low-certainty evidence); however, the impact on risk for *Clostridioides difficile* remains uncertain due to the low incidence of infection overall. Although gastric acid suppression appears likely to reduce the risk of gastrointestinal bleeding in patients at highest risk, it has no important impact on clinical outcomes such as length of hospital stay (**Option B**), length of ICU stay (**Option C**), mortality (**Option D**), or duration of mechanical ventilation.

KEY POINT

- Stress ulcer prophylaxis reduces the risk of gastrointestinal bleeding in high-risk critically ill patients but has no discernable impact on mortality or ICU or hospital lengths of stay.

Bibliography

Wang Y, Ye Z, Ge L, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis. BMJ. 2020;368:l6744. [PMID: 31907166] doi:10.1136/bmj.l6744

Item 85 Answer: A

Educational Objective: Assess asthma symptom control using a standardized, validated questionnaire.

The most appropriate next step in management is to administer a standardized, validated questionnaire such as the Asthma Control Test (**Option A**) to assess symptom control. Assessment of symptom control and risk is an essential component in the management of asthma and should be performed at each medical touchpoint. The Asthma Control Test and the Asthma Control Questionnaire are standardized, validated questionnaires that can discriminate between well-controlled and inadequately controlled asthma based on patient symptoms. These symptom control tools provide scores and cut points to distinguish different levels of control and to assess the patient's progress. When different systems are used to assess asthma control, the results broadly correlate but are not identical and using the same tool for each patient is most reasonable. Numerical asthma control tools are more sensitive to change in symptom control than categorical tools. In the Asthma Control Test, scores range from 5 to 25, with a higher score indicating better asthma control. Scores that correspond to other than well-controlled asthma suggest the need to review asthma risk factors, exposures, adherence, and inhaler technique, and the need for step-up therapy.

At present, fractional exhaled nitric oxide measurement (FeNO) (**Option B**) is not recommended to guide asthma treatment in the general population. Studies have demonstrated that FeNO-guided treatment reduces exacerbation rates compared with guideline-based treatment, but further studies are needed to identify the populations of patients most likely to benefit from FeNO-guided care and the optimal frequency of FeNO monitoring. For example, the 2020 Asthma Guideline Update from the National Asthma Education and Prevention Program conditionally recommends FeNO monitoring in patients with persistent allergic asthma, for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry as part of an ongoing asthma monitoring and management strategy. This patient does not need FeNO measurement.

Although a chest radiograph (**Option C**) is helpful in the initial evaluation of significant respiratory symptoms, it would not be indicated as routine care in a patient with controlled asthma symptoms.

The 6-minute walk test (**Option D**) provides a valid and reliable measure of exercise capacity in patients with lung disease. Patients walk at their own pace along a course for 6 minutes, and the total distance walked is recorded. The test can be used to assess response to therapy in patients with chronic respiratory disorders, especially pulmonary arterial hypertension, but there is no indication for this test in routine asthma care.

KEY POINTS

- Assessment of symptom control is an essential component in the management of asthma and should be performed using a standardized, validated questionnaire.
- At present, fractional exhaled nitric oxide measurement (FeNO) is not recommended to guide asthma treatment in the general population.

Bibliography

Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA. 2020;324:2301-2317. [PMID: 33270095] doi:10.1001/jama.2020.21974

Item 86 Answer: D

Educational Objective: Treat hypoxemic respiratory failure with oxygen by high-flow nasal cannula.

The most appropriate next step in managing this patient's hypoxemia is oxygen by high-flow nasal cannula (HFNC) (**Option D**). HFNC mixes and humidifies high-flow air and oxygen (30 L/min or more) to deliver a consistent F_{IO_2} (0.21-1.00) through a nasal cannula. The high flow creates positive airway pressure; the amount depends on the flow rate and cannot be measured or monitored consistently. A systematic review of oxygen delivered by HFNC versus standard oxygen therapy for hypoxemic respiratory failure showed that HFNC may decrease rates of endotracheal intubation and has no demonstrated effect on mortality.

Intubation and mechanical ventilation (**Option A**) are acceptable interventions to manage hypoxemic respiratory failure. However, alternative options such as HFNC and noninvasive ventilation may be preferable because they are less invasive and less prone to complications of therapy if monitored correctly. This patient can maintain gas exchange, has acceptable breathing effort (she is calm and is not using accessory muscles to breathe), and can communicate and cooperate. Thus, HFNC should be pursued first instead of intubation and mechanical ventilation.

Management of hypoxemic respiratory failure centers on administration of supplemental oxygen with the lowest possible F_{IO_2} necessary to meet oxygenation goals. A therapeutic target for peripheral arterial saturation (Sp_{O_2}) is between 90% and 96%, if feasible. This patient requires additional management to reach that therapeutic target; therefore, no change in hypoxemia management (**Option B**) is inappropriate.

Evidence favors the use of noninvasive positive pressure ventilation (NPPV) (**Option C**) in patients with COPD exacerbations, cardiogenic pulmonary edema, neuromuscular disease, and obesity hypoventilation syndrome and in patients who have been extubated, which places them at high risk of morbidity.

KEY POINTS

- In patients with hypoxemic respiratory failure, a therapeutic target for peripheral arterial saturation (Sp_{O_2}) is between 90% and 96%, if feasible.
- In patients with hypoxemic respiratory failure, high-flow nasal cannula may decrease rates of endotracheal intubation and does not affect mortality.

Bibliography

Rochwerg B, Einav S, Chaudhuri D, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. Intensive Care Med. 2020;46:2226-2237. [PMID: 33201321] doi:10.1007/s00134-020-06312-y

Item 87 Answer: D

Educational Objective: Treat COPD with smoking cessation.

Smoking cessation is the most appropriate additional therapy (**Option D**). Smoking cessation is essential in the management of COPD because it can slow the decline of FEV_1 and decrease mortality from COPD. The U.S. Preventive Services Task Force recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and approved pharmacotherapy to adult tobacco users. Combining behavioral counseling with pharmacotherapy is more effective than either modality alone. Effective counseling and behavioral resources include problem-solving guidance (e.g., developing a plan to quit and overcoming barriers), motivational interviewing, social support, and telephone quit lines. There is a dose-response relationship between the intensity and frequency of counseling and quit rates, which seems to plateau after 90 minutes of total counseling. All smokers without contraindications should additionally receive at least one of the FDA-approved treatments for smoking cessation, which include nicotine replacement medications, bupropion, and varenicline. Varenicline is superior to single forms of nicotine replacement therapy and bupropion. Moderate- and high-dose preparations of nicotine replacement therapy are more effective than lower-dose ones, and combining more than one type of nicotine replacement therapy (short-acting and long-acting) is more effective than monotherapy. Initiation of nicotine replacement therapy before smoking is stopped may also increase quitting success rates.

Macrolide antibiotics have anti-inflammatory and antimicrobial effects. Long-term macrolide therapy may reduce the frequency of exacerbations when prescribed to patients with severe COPD and a history of frequent exacerbations but do not result in slowing the decline in lung function or reduce the risk of death. Indication for macrolide use is in patients with COPD treated with combination long-acting β_2-agonist, long-acting muscarinic antagonist, and inhaled glucocorticoid who continue to have exacerbations, especially in those who are not current smokers. This patient does not have an indication for azithromycin (**Option A**) as he does not have frequent exacerbations.

Oral glucocorticoids (**Option B**) are recommended for short-duration treatment of acute exacerbations of COPD. However, long-term use of oral glucocorticoids does not slow the decline in lung function or reduce risk of death and should be avoided due to the risk of significant side effects, including diabetes and osteoporosis.

In patients with COPD, pulmonary rehabilitation (**Option C**) improves symptoms and quality of life and decreases frequency of hospitalizations, but it does not slow the decline in lung function or decrease mortality. It is recommended for patients with moderate to severe symptoms and for patients with at least one exacerbation per year. This patient does not have an indication for pulmonary rehabilitation.

KEY POINTS

- Smoking cessation is essential in the management of COPD because it is the only therapy that can slow the decline of FEV_1 and decrease mortality from COPD.
- All smokers without contraindications should receive at least one of seven FDA-approved treatments for smoking cessation.

Bibliography

Labaki WW, Rosenberg SR. Chronic obstructive pulmonary disease. Ann Intern Med. 2020;173:ITC17-ITC32. [PMID: 32745458] doi:10.7326/AITC202008040

Item 88 Answer: B

Educational Objective: Diagnose the cause of bronchiectasis.

The most appropriate diagnostic test to perform next is immunoglobulin measurement (**Option B**). This patient has symptoms and imaging findings consistent with bronchiectasis. Bronchiectasis is a chronic obstructive lung disease that results from enlargement of the airways, which leads to chronic inflammation, recurrent infection, and ineffective airway clearance. Bronchiectasis should be considered in the differential diagnosis of any patient with a chronic cough and mucopurulent sputum production. Other possible symptoms include hemoptysis, wheezing, and chest pain. Initial evaluation of patients with bronchiectasis should include testing for common causes, including abnormal immune function (by measuring immunoglobulin levels) and connective tissue disease. Patients should also be evaluated for other causes of bronchiectasis depending on their presentation, including cystic fibrosis, ciliary dysfunction, α_1-antitrypsin deficiency, aspiration, and allergic bronchopulmonary aspergillosis. All patients who can expectorate sputum should also be tested for chronic bacterial and mycobacterial infections to target for eradication or treatment during exacerbations. More than half of cases of bronchiectasis are considered idiopathic after a thorough evaluation.

Some patients with bronchiectasis require bronchoscopy with bronchoalveolar lavage (**Option A**) to test for chronic infections that may be missed in sputum cultures (including mycobacterial infections) or in patients who cannot expectorate. Bronchoscopy is not included in the initial diagnostic evaluation of bronchiectasis.

Common variable immunodeficiency is a heterogenous syndrome associated with decreased quantitative immunoglobulin levels and impaired humoral response to antigens. Impaired humoral response can be tested by measuring specific antibody production before and after immunization with tetanus and pneumococcal polysaccharide vaccines (**Option C**). Such testing is indicated in patients suspected of having a primary immunodeficiency disorder. However, the first step in this evaluation is documentation of low immunoglobulin levels.

Primary ciliary dyskinesia is an autosomal recessive genetic disorder that causes ineffective ciliary action in the respiratory tract, fallopian tube, and sperm cells. It can be diagnosed through genetic testing and nasal ciliary biopsy (**Option D**); a low nasal nitric oxide measurement can also support the diagnosis. Although nasal ciliary biopsy may be indicated for some patients, it would not be included in the initial diagnostic evaluation of bronchiectasis.

KEY POINTS

- Bronchiectasis should be considered in the differential diagnosis of any patient with a chronic cough, especially if the patient has a history of frequent respiratory infections or if the cough is productive.
- Initial evaluation of patients with bronchiectasis should include testing for common causes, including abnormal immune function (by measuring immunoglobulin levels) and connective tissue disease.

Bibliography

Hill AT, Sullivan AL, Chalmers JD, et al. British thoracic society guideline for bronchiectasis in adults. Thorax. 2019;74:1-69. [PMID: 30545985] doi:10.1136/thoraxjnl-2018-212463

Item 89 Answer: C

Educational Objective: **Treat hypersensitivity pneumonitis.**

The most appropriate management for this patient is to remove the pet parakeet from the environment (**Option C**). The patient's clinical and radiographic picture is consistent with a diagnosis of subacute hypersensitivity pneumonitis. The symptoms started soon after he acquired the pet parakeet. A comprehensive clinical history eliciting the temporal association of a specific exposure (avian antigen in this case) with symptom development suggests the diagnosis. The radiographic findings of micronodular opacities in the mid- and upper-lung zones are consistent with the diagnosis of subacute hypersensitivity pneumonitis. High-resolution CT scan of the chest typically reveals ground-glass opacities (faint opacification of the lung, as indicated by yellow arrows in the left panel below) and diffuse centrilobular micronodules (examples indicated by red arrows in the right panel below). Untreated, the disease can progress to a chronic form with the development of traction bronchiectasis and honeycomb changes. Removal of the offending antigen, if identified, is an essential and critical first step in the treatment of hypersensitivity pneumonitis. Elimination of the offending antigen reduces the risk of exacerbation as well as disease progression.

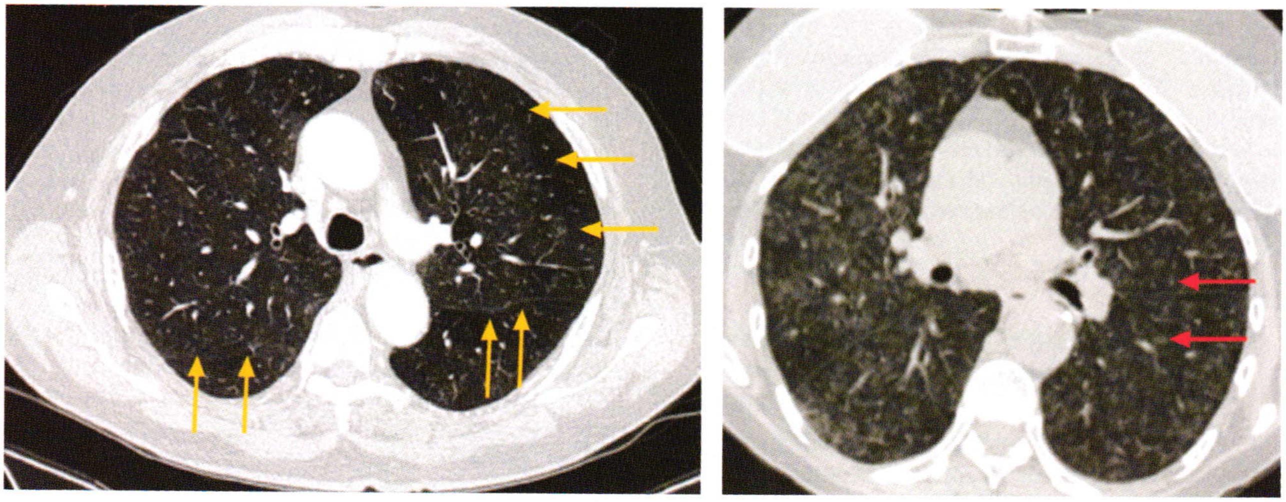
Early referral for lung transplant (**Option A**) is prudent in patients with idiopathic pulmonary fibrosis because the disease has a progressive course as well as potential for unpredictable and sudden decline. For hypersensitivity pneumonitis, lung transplant is an option for hypoxemic patients with severe disease that is refractory to conservative management strategies. Referral for lung transplant should not precede the removal of the offending antigen.

Nintedanib (**Option B**), a tyrosine kinase inhibitor, is an antifibrotic agent approved for the treatment of idiopathic pulmonary fibrosis. Although the fibrotic stage of hypersensitivity pneumonitis can mimic idiopathic pulmonary fibrosis radiologically, nintedanib does not have a current therapeutic indication for the management of hypersensitivity pneumonitis.

Surgical or transbronchial lung biopsy (**Option D**) may be required if the diagnosis remains uncertain. Typical histopathologic findings in early stages of hypersensitivity pneumonitis include lymphocytic cellular infiltration with poorly formed granulomas. Once fibrosis develops, the pattern may be histologically indistinguishable from the usual interstitial pattern seen in idiopathic pulmonary fibrosis. In this patient, the temporal relationship between antigen exposure and development of symptoms plus supportive imaging findings strongly suggest the diagnosis of hypersensitivity pneumonitis.

KEY POINTS

- The temporal association of a specific exposure with symptom development and ground-glass or centrilobular nodular opacities on high-resolution chest CT scan supports the diagnosis of hypersensitivity pneumonitis.
- An essential and critical first step in the treatment of hypersensitivity pneumonitis is identification and removal of the offending antigen.



ITEM 89

Bibliography

Fernández Pérez ER, Koelsch TL, Leone PM, et al. Clinical decision-making in hypersensitivity pneumonitis: diagnosis and management. Semin Respir Crit Care Med. 2020;41:214-228. [PMID: 32279292] doi:10.1055/s-0040-1701250

Item 90 Answer: E

Educational Objective: Treat alcohol intoxication.

The most appropriate management is supportive care (**Option E**) and monitoring for signs of alcohol withdrawal. The patient is intoxicated by the high alcohol concentrations found in hand sanitizer. Most sanitizers contain ethanol or isopropyl alcohol in concentrations generally above 60%. Ethanol and other ingested alcohols activate the γ-aminobutyric acid receptor, which is the primary central nervous system inhibitor; this in turn leads to central nervous system depression, including loss of consciousness and suppression of respiratory drive at high doses, which can lead to respiratory failure or aspiration events. Alcohol intoxication due to ethanol and isopropyl alcohol is managed with supportive care. The patient has a history of chronic alcoholism, and once the acute intoxication subsides, he should be monitored for signs of alcohol withdrawal. Withdrawal can begin within hours to days of the last ingestion and can be fatal.

Ethanol (**Option A**) has been used historically as a competitive inhibitor of alcohol dehydrogenase in the setting of methanol or ethylene glycol poisoning. It should not be given in the setting of ethanol toxicity and also has no role in isopropyl alcohol ingestion. When either methanol or ethylene glycol has been ingested, there is an increased anion gap metabolic acidosis as well as an increased osmolal gap that provides an important clue to the correct diagnosis. In this case the presence of an osmolal gap and normal anion gap support the diagnosis of isopropyl alcohol poisoning.

Flumazenil (**Option B**), a γ-aminobutyric acid receptor antagonist, is the antidote for benzodiazepine toxicity. It would not be expected to have any effect on outcomes in ethanol or isopropyl alcohol intoxication. There is reluctance to use flumazenil even in benzodiazepine overdose. Administration of flumazenil for suspected benzodiazepine overdose can reverse the effect of benzodiazepines leading to life-threatening central nervous system activation, including seizures, which are most likely in patients taking benzodiazepines chronically.

Fomepizole (**Option C**), an inhibitor of alcohol dehydrogenase, is used to slow the formation of toxic metabolites when methanol or ethylene glycol is ingested. It is the first-line agent for methanol or ethylene glycol ingestion. Intravenous ethanol is second-line treatment and also reduces toxic metabolite formation. Neither methanol nor ethylene glycol ingestion is suspected in this patient, so fomepizole is not appropriate.

Hemodialysis (**Option D**) can remove alcohols from the blood; it is usually indicated in the setting of methanol or ethylene glycol poisoning. However, hemodialysis is invasive and resource intensive and is generally not necessary for ethanol or isopropyl alcohol ingestion.

KEY POINTS

- Ethanol and isopropyl alcohol intoxication are managed with supportive care.
- Patients with underlying chronic alcoholism and acute ethanol or isopropyl alcohol toxicity should be monitored for signs of alcohol withdrawal.

Bibliography

Gallagher N, Edwards FJ. The diagnosis and management of toxic alcohol poisoning in the emergency department: A review article. Adv J Emerg Med. 2019;3:e28. [PMID: 31410405] doi:10.22114/ajem.v0i0.153

Item 91 Answer: D

Educational Objective: Diagnose a malignant pleural effusion.

The most likely diagnosis is malignant pleural effusion (**Option D**). The patient presented with increasing dyspnea in the setting of a new unilateral pleural effusion. The presence of heart failure, hepatomegaly and possible ascites, her occupational history, and her history of breast cancer broaden the differential diagnosis. Given the diagnostic uncertainty of the cause of the effusion, it should be sampled. The effusion was bloody in appearance and exudative by all three of Light's criteria (ratio of pleural fluid protein to serum protein >0.5, ratio of pleural-fluid lactate dehydrogenase [LDH] to serum LDH greater than 0.6, and pleural-fluid LDH greater than two thirds of the upper limit of normal for serum LDH). There are many causes of exudative effusions, but the most common are infection and malignancy. Given her history of breast cancer, the bloody appearance and exudative characteristic of the effusion make it highly suspicious for malignancy. While pleural fluid cytology is pending, it may not be very helpful. The sensitivity of pleural fluid cytology is approximately 60%, and some estimates suggest that it might even be lower (46%) when all types of malignancy are included. The sensitivity is highest for adenocarcinomas (79%) and lowest for mesothelioma (11%). Given the high suspicion of malignancy in this patient, additional testing should be pursued consisting of a repeat thoracentesis with cytology (if the first sample is negative) or thoracoscopic pleural biopsy.

Benign asbestos pleural effusions (**Option A**) can be bloody and are typically exudative, and they are seen in the context of asbestos exposure. However, benign asbestos pleural effusions are typically associated with pleural plaques not seen on this patient's radiograph.

Both heart failure (typically bilateral effusions) (**Option B**) and hepatic hydrothorax (**Option C**) (more often right sided) are serous effusions that are transudates and as such are excluded from this patient's differential diagnosis.

KEY POINTS

- The presence of one or more of Light's criteria is very sensitive in the diagnosis of an exudative effusion.
- The most common causes of exudative effusions are infection and malignancy.

Bibliography

Feller-Kopman D, Light R. Pleural disease. N Engl J Med. 2018;378:740-751. [PMID: 29466146] doi:10.1056/NEJMra1403503

Item 92 Answer: C

Educational Objective: Manage the progression of enteral feeding in a malnourished patient.

The most appropriate enteral feeding strategy for this patient is incrementally increasing to 1460 calories daily over 3 to 7 days (**Option C**). Patients with critical illness should receive early oral feeding when possible and should be considered at risk for malnutrition when they have not received nutrition for more than 48 hours. If oral nutrition is not feasible, early enteral nutrition is indicated to minimize infectious complications associated with delayed enteral nutrition. New guidelines suggest that, in malnourished patients, caloric and protein needs should be increased gradually to their goal over the course of 3 to 7 days to avoid risks associated with early refeeding syndrome. When patients are chronically malnourished or endure prolonged starvation, the body shifts from metabolizing carbohydrates to metabolizing protein and fat as the main source of adenosine triphosphate production. In the process, intracellular depletion of key electrolytes such as potassium, phosphorous, and magnesium begins to occur. When carbohydrates or other simple sugars are reintroduced to the diet or given intravenously, production of insulin causes rapid intracellular uptake and a rapid drop in extracellular concentrations of electrolytes. These shifts have potentially life-threatening consequences, including diaphragmatic weakness and respiratory impairment, tissue hypoxia, fatal arrhythmias, and cardiomyopathies. Guidelines suggest that enteral intake should be increased slowly over a period of 3 to 7 days. Should electrolyte levels markedly decrease from their baseline, suggesting refeeding syndrome, these abnormalities should be corrected and the number of calories the patient is receiving should be either reduced or held steady.

This patient should not receive either 1460 calories or 2000 calories daily (**Options A, B**) on the first day of nutritional supplementation as it may precipitate refeeding syndrome.

Guidelines indicate that full targeted medical nutrition therapy is considered to achieve more than 70% of the resting energy expenditure, but not more than 100%, to prevent overfeeding. Administering 2000 calories to this patient would represent overfeeding whether administered on the first day of feeding or over 3 to 7 days (**Option D**); therefore, it is not indicated.

KEY POINT

- Guidelines recommend that caloric and protein needs of critically ill patients at risk for refeeding syndrome should be gradually increased to their goal over the course of 3 to 7 days.

Bibliography

Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48-79. [PMID: 30348463] doi:10.1016/j.clnu.2018.08.037

Item 93 Answer: C

Educational Objective: Diagnose glucocorticoid-responsive asthma with fractional exhaled nitric oxide testing.

Fractional exhaled nitric oxide (FeNO) (**Option C**) will help predict this patient's responsiveness to inhaled glucocorticoids. Although FeNO should not be used as a diagnostic tool for asthma, it can be used to support this diagnosis in situations in which additional objective evidence is needed. FeNO may be useful if there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry as part of an ongoing asthma monitoring and management strategy. In adults with respiratory symptoms, FeNO levels above 50 ppb correlate with eosinophilic airway inflammation and predict response to inhaled glucocorticoids. FeNO levels below 25 ppb indicate that eosinophilic airway inflammation and glucocorticoid responsiveness are less likely; values between 25 and 50 ppb should be interpreted cautiously. In patients with asthma that is being treated with inhaled glucocorticoids, serial measurement of FeNO may help to monitor patient response to glucocorticoid therapy.

Bronchial challenge testing (**Option A**) is used to identify bronchial hyperresponsiveness, a diagnostic feature of asthma. This is particularly helpful in patients whose symptoms are suggestive of asthma but for whom other pulmonary function test results are normal. Patients inhale increasing doses of a substance known to induce bronchospasm, such as methacholine or histamine, in a stepwise fashion. This is followed by repeated measurements of FEV_1; if FEV_1 falls by 20% or more from the baseline value, the test is considered positive.

Diffusing capacity for carbon monoxide (DLCO) measurement (**Option B**) estimates the amount of gas transfer through the alveolar/capillary unit and is proportional to the surface area of a functional lung. DLCO is measured by inhalation of a gas mixture containing carbon monoxide and helium; the resulting value is corrected for hemoglobin level. DLCO is reduced in conditions in which functioning alveolar capillary units are destroyed, infiltrated, removed, or their function is compromised. Conditions that increase pulmonary capillary blood volume, such as pulmonary alveolar hemorrhage, left-to-right shunt, or asthma, can cause an elevation in DLCO. DLCO measurements do not predict responsiveness to glucocorticoids.

Pulse oximetry (**Option D**) provides a readily available noninvasive measurement of oxygen-bound hemoglobin in the circulation. A normal hemoglobin saturation measured by pulse oximetry is 95% to 100%, and values below 90% indicate hypoxemia. Pulse oximetry cannot predict responsiveness to glucocorticoids.

KEY POINTS

- In adults with respiratory symptoms, fractional exhaled nitric oxide levels above 50 ppb correlate with eosinophilic airway inflammation and predict response to inhaled glucocorticoids.
- Serial measurement of fractional exhaled nitric oxide may be helpful to monitor patient response to inhaled glucocorticoid therapy.

Bibliography

Jeppegaard M, Veidal S, Sverrild A, et al. Validation of ATS clinical practice guideline cut-points for FeNO in asthma. Respir Med. 2018;144:22-29. [PMID: 30366580] doi:10.1016/j.rmed.2018.09.014

Item 94 Answer: D

Educational Objective: Treat postoperative atelectasis with pain management.

Pain control is the most appropriate management (**Option D**) for this patient's atelectasis. The patient has postmastectomy pain that is impairing chest wall expansion, and she has developed atelectasis. Atelectasis is reported to occur in up to 90% of all anesthetized subjects, and it may persist for several days following surgery. Atelectasis can be the result of impaired respiratory mechanics after thoracic and abdominal surgeries resulting in shallow breathing patterns and avoidance of coughing. Atelectasis is associated with increased morbidity, including hypoxemia, retained secretions, and pneumonia. The management of atelectasis starts with focusing on the cause, in this case, pain. The patient is receiving inadequate pain control; the addition of multimodal pain control, which may include increased dosage of morphine, NSAIDs, acetaminophen, gabapentin, or nerve blocks, will improve pain control and chest expansion and may resolve the atelectasis. In addition to pain control, the application of chest physiotherapy is one of the first steps in management of atelectasis, if it can be tolerated by the patient.

For patients with atelectasis who fail to respond to pain control and chest physiotherapy, suctioning and bronchoscopy (**Option A**) may be of some value, particularly if secretions are tenacious and abundant. Bronchoscopy is not indicated in this patient who has yet to receive the most basic treatments.

There is no evidence that inhalation of aerosolized bronchodilators such as albuterol (**Option B**), salmeterol, or ipratropium are helpful in the resolution of atelectasis in a patient without airway disease. In addition, there is the possibility of adverse effects, drug interactions, and increased cost without evidence of benefit.

Although *N*-acetylcysteine (**Option C**) is frequently used, low-quality evidence from clinical trials has failed to demonstrate that either oral or inhaled *N*-acetylcysteine prevents or improves postoperative atelectasis; thus, it is not recommended.

KEY POINTS

- Postoperative atelectasis is associated with increased morbidity, including hypoxemia, retained secretions, and pneumonia, and may trigger the development of acute lung injury.
- In patients with postoperative atelectasis caused by pain, improved pain management should lead to decreased pain and increased chest expansion and may result in resolution of the atelectasis.

Bibliography

Odor PM, Bampoe S, Gilhooly D, et al. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. BMJ. 2020;368:m540. [PMID: 32161042] doi:10.1136/bmj.m540

Item 95 Answer: C

Educational Objective: Diagnose neuromuscular weakness as the cause of respiratory failure.

The most likely cause of this patient's respiratory failure is neuromuscular weakness (**Option C**) due to Guillain-Barré syndrome (GBS). Patients with GBS generally present with rapid onset of ascending, symmetric paralysis, and areflexia occurring over the course of 2 to 4 weeks, which may lead to respiratory failure. Specific components of pulmonary function testing can be helpful in the diagnosis of respiratory failure due to neuromuscular weakness. A greater than 20% decrement in forced vital capacity from the sitting to the supine position and maximal inspiratory and/or expiratory force less than 50% of predicted support the diagnosis of neuromuscular weakness–associated respiratory failure.

Decreased respiratory drive (**Option A**) leads to diminished alveolar CO_2 clearance. Patients often present with somnolence and difficulty protecting their airway. Sedating drugs (illicit or prescribed), anesthetics, and severe alcohol intoxication can lead to depressed central respiratory drive. Although this patient has hypercapnia, she is alert and cooperative and has no evidence of decreased respiratory drive.

Hypoxemic respiratory failure (**Option B**) is caused by inadequate oxygenation of hemoglobin. The most common causes of hypoxemic respiratory failure in the ICU are ventilation/perfusion mismatch and shunt, which occur when perfused areas of the lung are not ventilated, whether because of alveolar collapse (atelectasis) or filling of alveoli with blood, pus, protein, or water. An increased alveolar-arterial oxygen gradient is the key feature of ventilation/perfusion mismatch and shunt but is normal in this patient.

Pulmonary embolism (**Option D**) causes respiratory failure, primarily through ventilation/perfusion mismatch and to a less common extent through shunting or low mixed venous oxygen saturation. With shunting significant enough to cause hypoxemia, the alveolar-arterial gradient will be abnormal. Considering this patient's rapidly ascending paralysis, abnormal spirometry measures, and normal alveolar-arterial oxygen gradient, neuromuscular weakness is a more likely cause of her respiratory failure.

KEY POINT

- A greater than 20% decrement in forced vital capacity from the sitting to the supine position and maximal inspiratory and/or expiratory force less than 50% of predicted support the diagnosis of neuromuscular weakness–associated respiratory failure.

Bibliography

Newitt J, Strollo P. Breathing problems in adults with neuromuscular weakness. Am J Respir Crit Care Med. 2020;202:P31-P32. [PMID: 33258682] doi:10.1164/rccm.20211P31

Item 96 Answer: D

Educational Objective: Manage the discontinuation of antibiotic therapy in a patient with aspiration pneumonitis.

The most appropriate management is to discontinue antibiotics (**Option D**). In patients admitted to the ICU with acute respiratory failure and lower respiratory tract infiltrate, it is often difficult to determine whether the cause of the infiltrates is a bacterial infection or another source such as a viral infection or aspiration pneumonitis. Ultimately, the diagnosis of aspiration pneumonitis is clinical. Indicators include abrupt onset of respiratory symptoms following aspiration of gastric contents, low-grade fever, and infiltrates on chest imaging. The 2019 community-acquired pneumonia (CAP) guideline from the American Thoracic Society and the Infectious Diseases Society of America recommends standard empiric treatment for CAP in patients with suspected aspiration pneumonia. Many patients with aspiration pneumonitis experience rapid resolution of symptoms within 24 to 48 hours. In these patients, removal of antibiotics and supportive care alone is preferred. Because this patient improved clinically within 24 hours of admission, aspiration pneumonitis is likely and it is safe to discontinue therapy.

The 2016 Surviving Sepsis guidelines suggest that antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections associated with sepsis and septic shock but that shorter courses of antibiotics are reasonable in patients with rapid resolution of symptoms following sepsis and in patients who initially were thought to have sepsis but do not. An additional 4-, 7-, or 10-day course of antibiotics (**Options A-C**) is not needed in this patient.

KEY POINT

- Discontinuing antibiotic therapy is appropriate in patients who initially were thought to have sepsis but do not.

Bibliography

Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486-552. [PMID: 28098591] doi:10.1097/CCM.0000000000002255

Item 97 Answer: C

Educational Objective: Diagnose COPD with spirometry.

This patient has COPD (**Option C**). The diagnosis is supported by his significant smoking history combined with his symptoms, imaging, and spirometry findings. The possibility of COPD should be considered and spirometry should be performed in patients 40 years of age or older with progressive dyspnea, chronic cough, or chronic sputum production, particularly in the presence of known risk factors such as smoking.

COPD is a common disorder and is associated with high morbidity and mortality. However, the role of screening spirometry in asymptomatic persons with risk factors is controversial. The U.S. Preventive Services Task Force guideline and other guidelines recommend against screening for COPD in asymptomatic adults, whereas the Global Initiative for Chronic Obstructive Lung Disease (GOLD) advocates performing screening spirometry in persons with risk factors for COPD. The diagnosis of COPD is made using spirometric measurement to document airflow obstruction. COPD is confirmed by a postbronchodilator FEV_1/FVC ratio of less than 0.70.

Asthma (**Option A**) is an inflammatory disorder of the airways characterized by cough, wheezing, chest tightness, dyspnea, and variable airflow obstruction. Confirmation of reversible airflow obstruction is a cornerstone of asthma diagnosis and can be assessed by spirometry, with measurement of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio, or by serial measurement of peak expiratory flow rates. Airway obstruction that improves with bronchodilators, on subsequent measurements, or after 4 weeks of anti-inflammatory treatment supports a diagnosis of asthma. For adults, a significant change in FEV_1 is an increase from baseline of at least 12% and at least 200 mL. This patient does not have evidence of reversible airflow obstruction, excluding the diagnosis of asthma.

Bronchiectasis (**Option B**) should be considered in the differential diagnosis of any patient with a chronic cough, especially if the patient has a history of frequent respiratory infections or if the cough is productive of mucopurulent tenacious sputum. Bronchiectasis is diagnosed by high-resolution chest CT. Diagnostic criteria include airway diameter that is greater than that of its accompanying vessel and lack of distal airway tapering. This patient's clinical presentation is not consistent with bronchiectasis.

Desquamative interstitial pneumonia (DIP) (**Option D**) is a smoking-related diffuse parenchymal lung disease. Patients with DIP typically are symptomatic with a dry cough and dyspnea. DIP typically is associated with pure restrictive disease on spirometry. This patient's clinical presentation and spirometry results are not consistent with DIP.

KEY POINTS

- The possibility of COPD should be considered and spirometry should be performed in patients 40 years of age or older with progressive dyspnea, chronic cough, or chronic sputum production.
- The diagnosis of COPD is confirmed by an FEV_1/FVC ratio of less than 0.70 without a significant bronchodilator response.

Bibliography

Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. N Engl J Med. 2019;381:1257-1266. [PMID: 31553837] doi:10.1056/NEJMra1900500

H

Item 98 Answer: D

Educational Objective: Diagnose pulmonary hypertension due to left-sided heart failure.

The most likely diagnosis is left-sided heart failure (**Option D**) leading to pulmonary hypertension (PH). PH occurs when a patient's pulmonary artery pressure is elevated. Normal mean pulmonary artery pressure in adults is rarely greater than 20 mm Hg. Accordingly, the Sixth World Symposium on Pulmonary Hypertension (WSPH) has defined PH as mean pulmonary pressure greater than 20 mm Hg. The WSPH has further classified PH into five groups based on the clinical, epidemiologic, and histologic profiles. PH related to left-sided heart disease (group 2) accounts for 65% to 80% of all PH diagnoses. This patient has several risk factors that support underlying left-sided heart disease, including advanced age, history of hypertension, diabetes, and coronary artery disease. The presence of orthopnea, elevated jugular venous pressure, an S_3, pulmonary congestion on chest radiography, and echocardiographic evidence of reduced ejection fraction support the diagnosis of PH related to left-sided heart disease.

Chronic thromboembolic pulmonary hypertension (CTEPH) (group 4) (**Option A**) is uncommon, even in patients with a history of venous thromboembolism. Approximately 20% of patients with CTEPH report no previous deep venous thrombosis or pulmonary embolism. This patient's history, physical examination, and echocardiographic findings support left-sided heart failure as the cause of PH.

In patients with pulmonary arterial hypertension (group 1) (**Option B**), the lung parenchyma usually appears normal on chest imaging. This patient has pulmonary vascular congestion on chest imaging.

This patient has findings of left-sided heart failure and no clinical or radiographic findings to suggest interstitial lung disease (**Option C**).

KEY POINTS

- Pulmonary hypertension (PH) related to left-sided heart disease accounts for 65% to 80% of all PH diagnoses.

(Continued)

KEY POINTS *(continued)*

- The diagnosis of pulmonary hypertension due to left-sided heart disease can usually be made by physical examination, chest radiography, and echocardiography.

Bibliography

Vachiéry JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. Eur Respir J. 2019;53. [PMID: 30545974] doi:10.1183/13993003.01897-2018

Item 99 Answer: C

Educational Objective: Evaluate a 7-mm solitary pulmonary nodule in a patient with low risk.

The most appropriate next step in management is chest CT in 6 months (**Option C**). The patient has an indeterminate lung nodule that is 7 mm in size; the first step in evaluation is to estimate the probability of malignancy. This can be done qualitatively or quantitatively with risk prediction calculators. Calculating the probability of malignancy is most useful in treating nodules that are 8 to 30 mm in diameter nand helps to determine subsequent testing and diagnostic strategy. One commonly used risk calculator is the Brock model (www.brocku.ca/cancerpredictionresearch). This model considers the following as risk factors: older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count (one to four nodules is associated with a higher risk of malignancy, whereas five or more is associated with a lower risk of malignancy), and spiculation. A low-risk nodule measuring 6 to 8 mm should be monitored with serial CT, the first CT examination in 6 to 12 months, and then CT at 18 to 24 months can be considered.

For solitary solid noncalcified nodules larger than 8 mm in diameter, the Fleischner Society guideline recommends consideration of a 3-month follow-up, work-up with combined PET/CT, tissue sampling, or a combination thereof (**Options A, B**); any one of these options may be appropriate depending on size, morphology, comorbidity, and other factors. This patient with a 7-mm low-risk nodule does not require any of these interventions or surgical resection (**Option D**) given the low probability that the nodule is malignant.

KEY POINT

- For a low-risk, solitary solid pulmonary nodule measuring 6 to 8 mm, repeat CT evaluation in 6 to 12 months is recommended.

Bibliography

MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

H

Item 100 Answer: B

Educational Objective: Diagnose fat embolism syndrome.

The most likely diagnosis is fat embolism syndrome (**Option B**), a rare but potentially lethal complication resulting from systemic manifestations of fat emboli. Most commonly associated with long bone and pelvic fractures, fat embolism syndrome can also be associated with nontraumatic conditions such as pancreatitis, osteomyelitis, and lipid infusion. It is a clinical diagnosis centered on the triad of respiratory insufficiency, neurologic dysfunction, and petechial rash in an appropriate clinical setting. Although not always present, the petechial rash is characteristically located on nondependent parts of the body such as the neck and chest. Onset of fat embolism syndrome typically occurs between 24 and 72 hours after a fracture but may occur as early as 12 hours after. Chest radiographs may be normal. Chest CT findings are nonspecific and primarily parenchymal; bilateral well-demarcated ground-glass opacities or ill-defined centrilobular nodules may be noted. Fat has low attenuation, and it is uncommon to find filling defects on CT angiography. Treatment is supportive, and most patients with fat embolism syndrome fully recover, although estimates of mortality range from 5% to 20%.

Air embolism (**Option A**), a potentially lethal illness, results from the introduction of air into the vasculature. Air embolism can also have respiratory and neurologic manifestations; however, a rash is unusual. Additionally, symptoms of air embolism develop immediately after the inciting event. A variety of mechanisms are responsible for air embolism, including neurosurgical and otolaryngologic surgical procedures, penetrating leg wounds or blunt chest trauma, insertion of vascular catheters, and barotrauma associated with positive pressure ventilation.

Hospital-acquired pneumonia (HAP) (**Option C**), by definition, develops more than 48 hours after admission and is not the correct diagnosis in this patient with symptoms and pulmonary infiltrates within 24 hours of admission. Additionally, HAP cannot account for the petechial rash.

Pulmonary embolism (**Option D**) manifests with tachypnea, respiratory distress, and hypoxia. However, neurologic symptoms and rash are not seen in patients with pulmonary embolism. CT angiography in pulmonary embolism reveals intraluminal filling defects.

KEY POINTS

- Fat embolism syndrome is most commonly associated with long bone and pelvic fractures but can also be associated with nontraumatic conditions such as pancreatitis, osteomyelitis, and lipid infusion.
- Clinical diagnosis of fat embolism syndrome is centered on the triad of respiratory insufficiency, neurologic dysfunction, and petechial rash in the appropriate clinical context.

Bibliography

Newbigin K, Souza CA, Torres C, et al. Fat embolism syndrome: State-of-the-art review focused on pulmonary imaging findings. Respir Med. 2016; 113:93-100. [PMID: 26895808] doi:10.1016/j.rmed.2016.01.018

H

Item 101 Answer: C

Educational Objective: Treat chronic thromboembolic pulmonary hypertension.

The most appropriate treatment for this patient with chronic thromboembolic pulmonary hypertension (CTEPH) is referral for surgical thromboendarterectomy evaluation (**Option C**). CTEPH consists of organized, chronic thrombi within the pulmonary arterial system. Patients with CTEPH demonstrate both mechanical obstruction of pulmonary arteries and features of disordered pulmonary angiogenesis, fibrinolysis, and vascular remodeling. These changes manifest in increased pulmonary vascular resistance and elevated mean pulmonary artery pressure. Untreated, CTEPH can lead to right-sided heart failure and death. Lifelong anticoagulation to help prevent further thromboembolism and consideration of thromboendarterectomy are indicated for CTEPH. The only potentially curative therapy for CTEPH is pulmonary thromboendarterectomy. Because the disease is usually progressive, surgical evaluation at an experienced center is warranted in all patients with CTEPH, regardless of disease severity. Approximately half of patients with CTEPH will be eligible for surgery. Pulmonary thromboendarterectomy can result in normalization of pulmonary hemodynamics in about one third of patients who undergo surgery.

For patients who are not candidates for surgical intervention or who choose not to pursue this path, medical therapy is indicated. Currently, the only medication approved for treating CTEPH is riociguat (**Option A**), a stimulator of soluble guanylate cyclase, the primary receptor for nitric oxide.

Balloon pulmonary angioplasty (**Option B**) may be appropriate for some nonoperative patients. Balloon pulmonary angioplasty is an emerging field. A catheter-directed balloon is inserted into the pulmonary artery and inflated to improve blood flow and reduce vascular resistance within the pulmonary circulation. Neither riociguat nor balloon pulmonary angioplasty should be offered before considering surgical intervention. In patients with inoperable CTEPH and those who have persistent pulmonary hypertension following thromboendarterectomy, balloon pulmonary angioplasty or medical therapy with riociguat should be considered.

No further treatment (**Option D**) is inappropriate for this patient. Lifelong anticoagulant therapy is indicated in all patients to prevent further thromboembolism, but because the disease is progressive without intervention, evaluation for surgical thromboendarterectomy is important.

KEY POINTS

- Anticoagulation and consideration of thromboendarterectomy are indicated for all patients with chronic thromboembolic pulmonary hypertension.

(Continued)

KEY POINTS ***(continued)***

- In patients with inoperable chronic thromboembolic pulmonary hypertension and those who have persistent pulmonary hypertension following thromboendarterectomy, balloon pulmonary angioplasty or medical therapy with riociguat should be considered.

Bibliography

Sahutoglu E, Tuncay E, Aras G, et al. Chronic thromboembolic pulmonary hypertension in patients with persistent chest symptoms after acute pulmonary embolism. Anatol J Cardiol. 2021;25:24-29. [PMID: 33382052] doi:10.14744/AnatolJCardiol.2020.69057

Item 102 Answer: C

Educational Objective: Treat an asthma exacerbation.

The most appropriate management for this patient with an asthma exacerbation is to start a 5-day course of prednisone (**Option C**). Asthma exacerbation is an acute worsening of symptoms or lung function from baseline that necessitates a step up in therapy. Prompt recognition and treatment of asthma exacerbations are needed to relieve symptoms and prevent hospitalizations. All patients with asthma should have a written asthma management plan that helps them recognize the symptoms of an exacerbation and begin self-treatment. If symptoms do not improve with self-treatment, evaluation is appropriate. Clinicians should screen for patient factors that contribute to an increased risk of death from asthma and should counsel patients appropriately. Important risk factors include a history of near-fatal asthma attack or intubation; an emergency department or hospital visit in the last 12 months; poor asthma medication adherence or not using inhaled glucocorticoid; current or recent treatment with an oral glucocorticoid; psychosocial stressors or psychiatric disease; food allergy; and overuse of a short-acting β_2-agonist. On physical examination, signs of a severe asthma exacerbation that should prompt aggressive intervention and hospitalization include being unable to speak in full sentences; use of accessory muscles of respiration; respiration rate greater than 30/min, heart rate greater than 120/min; oxygen saturation less than 90% with the patient breathing ambient air; and agitation, confusion, or drowsiness. This patient does not have any signs of or risk factors for a severe asthma exacerbation; therefore, she can be safely managed as an outpatient. The best next step is to begin an oral glucocorticoid such as prednisone for a period of 5 to 7 days.

Asthma exacerbations do not require antibiotics (**Option A**) unless other signs suggestive of infection, such as fever, are present.

Patients such as this one with low risk for a severe asthma exacerbation can be treated with a 5- to 7-day course of prednisone. A 14-day course of prednisone (**Option D**) is unnecessarily long, and intravenous glucocorticoids, such as methylprednisone, followed by a course of prednisone (**Option B**) is also excessive and unnecessary.

The patient has already stepped up her maintenance therapy without resolution of her symptoms; therefore, changing her therapy from budesonide to budesonide-formoterol (**Option E**) is unlikely to be effective.

KEY POINTS

- All patients with asthma should have a written asthma management plan that helps them recognize the symptoms of an exacerbation and begin self-treatment.
- Patients with an asthma exacerbation who continue to have symptoms after self-treatment should be treated with an oral glucocorticoid.

Bibliography

Fergeson JE, Patel SS, Lockey RF. Acute asthma, prognosis, and treatment. J Allergy Clin Immunol. 2017;139:438-447. [PMID: 27554811] doi:10.1016/j.jaci.2016.06.054

Item 103 Answer: B

Educational Objective: Treat exacerbation of bronchiectasis.

The most appropriate management is ciprofloxacin (**Option B**). In patients with bronchiectasis, the presence of chronic symptoms of cough and sputum production typically indicates irreversible airway dilation. Treatment of the underlying cause may not lead to improvement in current symptoms but could prevent further progression. Otherwise, treatment of bronchiectasis focuses on airway clearance and preventing and treating exacerbations. This patient is experiencing a bronchiectasis exacerbation, which is often characterized as a change in sputum volume, viscosity, or purulence; increased cough; wheezing; shortness of breath; hemoptysis; or decline in lung function. In addition to continuing airway clearance therapies with albuterol and hypertonic saline nebulization, exacerbations of bronchiectasis are treated with antibiotics tailored by previous sputum culture results. If sputum culture results are not available, empiric antibiotic therapy is recommended, often with a fluoroquinolone, to ensure *Pseudomonas* coverage until sputum culture results are available. The standard course of antibiotics for a bronchiectasis exacerbation is 14 days, but shorter courses may be used for mild bronchiectasis in the absence of *Pseudomonas aeruginosa*. This patient has previously grown *P. aeruginosa* and should begin taking an antibiotic with appropriate coverage, such as ciprofloxacin.

Although azithromycin (**Option A**) is commonly used for community-acquired pneumonia and COPD exacerbations, it has inadequate coverage for *P. aeruginosa*. Of note, azithromycin can be used for long-term treatment in some patients with bronchiectasis and frequent exacerbations to reduce airway inflammation. When deciding whether to use macrolide antibiotics, the physician should weigh the risk of future exacerbations against the possibility of developing macrolide resistance.

Inhaled dornase alfa (**Option C**) is used in patients with cystic fibrosis to reduce sputum viscosity; it improves

H
CONT.

lung function and decreases the frequency of exacerbations. However, it is potentially harmful in patients with non–cystic fibrosis bronchiectasis, as patients who were treated with it had more frequent exacerbations, hospitalizations, and antibiotic and glucocorticoid courses than those who received placebo. Thus inhaled dornase alfa is not routinely used for management of bronchiectasis exacerbations.

Glucocorticoids (**Option D**) are not indicated in the treatment of bronchiectasis exacerbations in the absence of concomitant asthma or COPD, although they may be used in some patients with significant bronchospasm. This patient has no indication for glucocorticoids.

KEY POINTS

- In addition to continuing airway clearance, bronchiectasis exacerbations are treated with antibiotics tailored by previous sputum culture results.
- If sputum culture results are not available, empiric antibiotic therapy is recommended, often with a fluoroquinolone.

Bibliography

Hill AT, Sullivan AL, Chalmers JD, et al. British thoracic society guideline for bronchiectasis in adults. Thorax. 2019;74:1-69. [PMID: 30545985] doi:10.1136/thoraxjnl-2018-212463

Index

Note: Page numbers followed by f and t denote figure and table, respectively.
Test questions are indicated by Q.

A
ABCDEF Care Bundle, 60t
Abdominal aortic aneurysm, 87t
Abdominal surgical emergencies, 86–87, 87t
Abruptio placentae, 88t
Acetaminophen toxicity, 86t
Acetazolamide, 56, 57t
Acetylcholine receptor antibody tests, 50
Aclidinium, 12t, 19t
Active internal rewarming, Q79
Acute cardiogenic pulmonary edema, 70–71
Acute fatty liver of pregnancy, 88t
Acute hypercapnic respiratory failure, 61, 72–75, 72t, 73t
Acute inhalational injuries, 68–69
Acute interstitial pneumonia, 25t, 26t, 31
Acute mountain sickness, 56–57
Acute Physiology and Chronic Health Evaluation, 58
Acute respiratory distress syndrome (ARDS), 67t, 69–70, 69t
  acute interstitial pneumonia *versus*, 31
  amiodarone toxicity and, 28
  causes of, 69t
  definition of, 70t
  diagnosis of, Q21
  DPLD and, 26t
  nonventilatory management in, 70
  in pregnancy, 88t
  radiographic findings in, 67t
  treatment of, Q48
  ventilatory management in, 69–70
Acute respiratory failure, 67–75, 67f
Acute upper airway management, 67–68
Adaptive servo-ventilation, 55, 56t
Adenocarcinomas, 39, 46–47, 47t
Adenoid cystic carcinoma, 49
Adenosine deaminase, 39
Air pollution
  asthma risk and, 7
  COPD risk and, 15
Air travel
  preflight screening, 58t
  pulmonary disease and, 57–58, 57t
  safety for COPD patients, Q82
Airway edema, 68
Albuterol, 11, 12t, 19t, Q6
Alcohol poisoning, 82–83, 83t, Q90
Alkylating agents, PAH and, 43t
Allergic asthma, 8, Q24
Allergic bronchopulmonary aspergillosis, 9, 23t
Alveolar damage, 29t, 69f
Ambrisentan for PAH, 44t
Aminophylline, 19t, 20
Aminorex, 43t
Amiodarone, lung toxicity of, 28, 29t
Ammonia, inhaled exposure to, 69t
Amniotic fluid emboli, 88t
Analgesia in critical care patients, 59–60, 59t
Anaphylaxis, 80–81, 80t, Q41
Anaplastic lymphoma kinase receptor tyrosine kinase (*ALK*) translocation, 48
Anemia, 35, Q76
Angioedema, 80–81
Angiotensin, selection of, 66t
Anoxic brain injury, 88–89
Antibiotics, in sepsis, 78–79, Q18, Q96
Antihistamines, toxicity of, 84t, 86t
Anti-inflammatory agents, adverse effects of, 19t
Anti-Parkinson agents, toxicity of, 84t
Antisynthetase syndrome, 27
α_1-Antitrypsin, 15–17, 20
Antitussives, 20
Apnea-hypopnea index (AHI), 52–54
Appendicitis, 87t
Arformoterol for asthma, 12t
Asbestos-related pleuropulmonary disease, 34t, 50t, Q23
Ascending cholangitis, Q60
Ascites, respiratory mechanics and, 74
Aspergillosis, 9, 23
Aspergillus spp., 9, 23
Aspiration, bronchiectasis caused by, 22, 23t
Aspiration pneumonitis, Q96
Aspirin-exacerbated respiratory disease, 9
Asthma, 5–15
  airway resistance and, 74–75
  bronchial challenge testing, 7–8, Q17
  chronic, 9–14
  comorbidities, 11t
  controller medications, 13–14
  epidemiology of, 5–7
  exacerbations, 14, 14t, Q102
  fractional exhaled nitric oxide, Q93
  GERD and, 11, Q80
  management of, 9, 10f, 12t, 14, Q6, Q13, Q85, Q102
  natural history of, 5–7
  pathogenesis of, 7
  in pregnancy, 15
  refractory, 14–15
  risk factors for, 7
  symptoms of, 7–9, Q85
Asthma Control Test, 9, Q85
Asthmatic triad, 7
Atelectasis, 38t, 71, Q91, Q94
Atrial fibrillation, in PAH, 43–44
Atropine toxicity, 84t
Azithromycin, 22, Q14, Q50, Q75

B
Bakers' asthma, 8, Q43
Bath salts, antidotes for, 85t
Beclomethasone, 12t, 19t, Q6
Benfluorex, 43t
Benign pleural effusions, 39–40
Benralizumab, 12t, 13
Benzodiazepines, 59–60, 81t, 82, 85t, 86t
Bilevel positive airway pressure (BPAP)
  for cardiogenic pulmonary edema, 71
  for COPD, 55, 74, Q67
  effects and indications, 62, 63t
  in neuromuscular diseases, 56, 56t
  for obesity hypoventilation syndrome, 55, 73, Q49
  for obstructive sleep apnea, 53–54
Bleomycin, lung toxicity of, 29t
BODE index, 15, 16, 17t, 21
Bosentan for PAH, 44t
Bosutinib, 43t
Bowel distention, respiratory mechanics and, 74
Bowel obstruction, 24, 87t
Bromocriptine, 81t, 82
Bronchial cast formation, 68
Bronchial challenge testing, 1, 7–8, Q17
Bronchial hyperreactivity, 7–9
Bronchial thermoplasty, 6t, 14
Bronchial wall thickening, 23
Bronchiectasis, 22–24, 23f, 23t, Q88, Q103
Bronchoconstriction, 8, 68, Q40
Bronchodilators, 7, 18–20, 18t, 19t, Q8
Bronchoscopy, 3–5, 6t, 49, 71, Q9
Bronchospasm, 1, 9, 12t, 19t, 69t
Budesonide, 11, 12t, 19t
Budesonide-formoterol, 13, Q13, Q40

Burn injuries, 68, 69t, Q9
Busulfan, lung toxicity of, 29t

C
Caffeine toxicity, 84t
Calcium channel blockers, 43–44, 44t, 86t
Cancer, pleural effusions in, 39. *See also* Lung cancers
Cannabinoids, antidotes to, 85t
Capnometry, 55
Carbamate toxicity, 84t
Carbon monoxide poisoning, 62, 83–84
Carboxyhemoglobin, 83–84
Carcinoid tumors, 49–50
Cardiogenic shock, 76–77, 76t
Cardiovascular disease, sleepiness and, 51
Central line-associated bloodstream infections, 61t
Central sleep apnea (CSA) syndromes, 54–55, Q62, Q66, Q74
Central venous access, 65t
Cerebral edema, high-altitude-related, 57
Charcot triad, Q60
Chemical injuries, 68, 69t
Chest radiography, 4, 4t
Cheyne-Stokes breathing, 54, 55
Chlorine, inhaled exposure to, 69t
Cholangitis, 87t, Q60
Cholecystitis, 87t
Cholesterol, pleural fluid, 37, 38t
Cholinesterase inhibitors, inhaled exposure to, 69t
Choosing Wisely® campaign, 61
Chronic beryllium disease (CBD), 34t
Chronic nocturnal hypoxia, 45
Chronic obstructive pulmonary disease (COPD), 15–22
  acute exacerbations, 21–22
  air travel safety for patients with, Q82
  airway resistance and, 74–75
  assessment, 16–17
  azithromycin for, 18t, 22, Q14, Q75
  comorbid conditions, 16
  diagnosis, 16
  epidemiology of, 15
  exacerbation with glucocorticoids, Q64
  heterogeneity of, 15–16
  lung volume reduction surgery in, 21, Q44
  management of, 17–21, 18t, 19t, Q8, Q87
  oxygen therapy for hypoxemia, Q11
  pathophysiology of, 15
  prevention of exacerbations, 22
  prognosis in, 17t
  pulmonary rehabilitation for, 20, Q63
  risk factors for, 15
  roflumilast for, 18t, 19t, 20, 22, Q14, Q50
  severity of, 17t
  sleep-related hypoventilation and, 55
  smoking cessation in, 17, 22, Q87
  spirometry use and, Q97
Chronic thromboembolic pulmonary hypertension (CTEPH), 44–45, Q10, Q101
Chylothorax, 37t, 39, Q32
Ciclesonide, 12t, 19t
Circadian rhythm disruption, 51t, 52
Clubbing, 23, 30, 48f, 68, Q30, Q33
Cocaine, 43t, 84t, 85t
Cognitive impairment, long-term, 66
Coma, 87–88, 89t
Combined pulmonary fibrosis and emphysema (CPFE), 31, 32f, Q5
Common variable immunodeficiency, 23t
Computed tomography (CT)
  of the chest, types, 4–5, 4t
  DPLD diagnosis using, Q26, Q33
  lung cancer evaluation using, Q51
  pulmonary imaging, 3–5
  for pulmonary nodule evaluation, 4, Q99
Confusion Assessment Method-ICU, 60
Connective tissue disease (CTD), 26, 27, 28t, Q83
Constrictive pericarditis, 38t, 76t
Continuous positive airway pressure (CPAP), 56t, 63t
Cor pulmonale, 20, 26
Cough-variant asthma, 8
Critical care medicine. *See also* Intensive care units (ICUs)
  blood pressure support, 65–66
  common ICU conditions, 67–80
  complications, 66–67
  delirium prevention in, 60, Q1
  early mobilization in, 60, 61, 66, Q1
  hemodynamic support, 63
  hyperoxia prevention in, Q45
  intravenous access, 63–64, Q59
  nutritional support in, 60, Q73
  organization of, 58–59
  patient evaluation in sepsis, Q55
  pleural effusion in, Q71
  point-of-care ultrasonography, 75, 77, Q28
  post-intensive care syndrome, 67
  principles of, 59–67
  respiratory support, 61–62
  sedation in, 59–61, 70, Q31
  stress ulcer prophylaxis, 59, Q84
Critical illness myopathy, 66, 67t, 72t
Critical illness neuromyopathy, 67t
Critical illness polyneuropathy, 66, 67t
Cryptogenic organizing pneumonia (COP), 31
Crystalloid solution, sepsis treatment with, 61, 78, Q35
CURB-65, 58
Cushing syndrome, 48
Cyanide poisoning, 84–85
Cystic fibrosis (CF), 23t, 24–25, 40t, Q56
Cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, 24, Q56
Cysts, bronchial, 23

D
Dantrolene, 38t, 81t, 82, Q65
Dasatinib, 38t, 43t
Dead space, increased, 72–74, 72t
Decreased respiratory drive, 72, 72t, 73
Delirium, 60, 60t, Q1
Depression, montelukast-associated, Q58
Dermatomyositis, 28t
Desquamative interstitial pneumonia (DIP), 25t, 26t, 27
Dexfenfluramine, 43t
Dexmedetomidine, 59, 59t
Dextromethorphan antidotes, 85t
Diaphragm, ultrasonography of, 5
Diet, asthma care and, 14
Diffuse parenchymal lung disease (DPLD), 25–33, Q20
  causes of, 27–31
  classification of, 25t
  connective tissue diseases and, 28t
  CT scanning, 26–27
  diagnosis, 25–27, 26t, Q26
  drug-induced, 28, 29t
  features of occupational lung disease, 34t
  ICU and, 71
Digoxin toxicity, 86t
Distributive shock, 66t, 76, 76t
Diuretics for PAH, 43–44
Dobutamine, 66t, 78
Dopamine, 66t, 78
Drugs of abuse, 85–86, 85t
Dupilumab, 12t, 14
Dust-related pneumoconiosis, 34t
Dysautonomia, 74, 82
Dyspnea scale, 15, 16t, 17t

E
Echocardiography, 41, 42f, 75, 88t, Q37, Q72
E-cigarette or vaping-associated lung injury (EVALI), 68–69
Eclampsia, 88t
Ectopic pregnancy, 87t
Edrophonium toxicity, 84t
Electromyogram testing, 66
Emphysema, 16, 20, 21, 31, 32f, Q5, Q44. *See also* Chronic obstructive pulmonary disease (COPD)
Empyema, 14f, 14t, 38t, 39
Encephalopathy, 87–89
Endobronchial carcinoids, 49f
Endobronchial ultrasonography, 5, 6t
End-organ hypoperfusion, 75, 75f
Endothelin-1 antagonists, 44t
Endotracheal intubation, airway protection in, Q42
Enteral nutrition, 60, 79–80, Q73, Q92
Eosinophilia, 3, 7–9, 13–14, 25t, 29t
Ephedrine toxicity, 84t
Epidermal growth factor receptor *(EGFR)* mutation, 47
Epinephrine, 66t, 78, 80t, Q41

Epoprostenol for PAH, 44t
Epworth Sleepiness Scale, 45, 51
Ethanol, 83, 83t
Ethylene glycol, 83, 83t, Q54
Evidence-based care protocols, 59
Excessive daytime sleepiness, 51–52, 51t
Exercise
    6-minute walk test, 2
    asthma care and, 14
    pulmonary rehabilitation, 20
Exercise-induced bronchoconstriction (EIB), 8, Q40
Extubation, 62–63, 64t, 65t

F
Fat embolism, 69, 87, Q100
Fenoterol, adverse effects of, 19t
Fentanyl, 84t, 85t
Fluid resuscitation, 76, 78
Flumazenil, 85
Flunisolide for asthma, 12t
Fluticasone, 12t, 19t, 88t
Fomepizole, 83, 83t, Q54
Formoterol, 10t, 11, 12t, 19t, Q6, Q13
Fractional exhaled nitric oxide (FeNO), 3, 7, Q93

G
Gastroesophageal reflux disease (GERD), 11t, Q80
Gastrointestinal bleeding, Q53
Germ cell tumors, 50
Glasgow Coma Scale, 87, 89t
Glucocorticoids
    in asthma treatment, 10f, 12t, 13–15
    for COPD exacerbation, Q64
    inhaled, 13, 20, 23, Q6
    oral, 20
    for refractory septic shock, Q57
Glucose intolerance, sleepiness and, 51
Glycopyrrolate, 12t, 19t
GOLD model, 17t, 21, Q50
Gottron papules, 26
Guillain-Barré syndrome, 74, Q95

H
Haemophilus influenzae, 22
Haldane effect, 73, 74
Hallucinogens, antidotes for, 85t
Haloperidol, 82
Hamartomas, 49
Heart failure, 38t, 41, 70–71, Q78, Q98
Heat stroke, 81, 81t, Q4
Hemodialysis, Q54
Hemorrhages, 6t, 28t, 72, 76, 88t, Q53
Hepatitis C antiviral therapies, 43t
Heroin, 84t, 85t
High resolution CT (HRCT), 26–32, 26t, Q26
High-altitude cerebral edema, 57
High-altitude pulmonary edema (HAPE), 57, Q34
High-altitude-related illnesses, 56–58, 57t
High-flow nasal cannulas (HFNC), 62, Q86
HIV, bronchiectasis caused by, 23t
Honeycombing, 25t, 30, 30f, Q33
Hospice care, decision making on, 21
Hour-1 care bundle for sepsis, 61t, Q68
Hypercapnic respiratory failure, 72–73, 72t, 73t
Hyperoxia, prevention in critical care, Q45
Hypersensitivities, 23t, 27–28
Hypersensitivity pneumonitis (HP), 27–28, 34t, Q89
Hypertension
    glucocorticoids and, 12t, 19t
    obstetric emergencies, 88t (*See also* Portopulmonary hypertension; Pulmonary arterial hypertension (PAH); Pulmonary hypertension (PH))
Hyperthermic emergencies, 81–82, 81t
Hypertrophic pulmonary osteoarthropathy (HPOA), 48f
Hyperventilation, 54
Hypoalbuminemia, 35t, 38t
Hypoglossal nerve simulator, 54
Hyponatremia, paraneoplastic, 48
Hypoperfusion, clinical signs of, 75f
Hypopneas, 52
Hypothermia, 82, 82t, Q79
Hypovolemic shock, 76, 76t
Hypoxemia, 61, Q11, Q46
Hypoxemic respiratory failure, 68, 71, Q86

I
ICU. *See* Critical care medicine; Intensive care units (ICUs)
ICU care bundles, 60t, 61, 61t
ICU-acquired weakness, 66, 67t, 73
Idiopathic hypersomnia, 51
Idiopathic pulmonary fibrosis (IPF), 25t, 26t, 30, 30f, Q30, Q33
Iloprost for PAH, 44t
Immunizations for COPD patients, 20
Immunoglobulin measurement, Q88
Immunosuppression for NSIP, 30–31
Inappropriate antidiuretic hormone secretion, 48
Indacaterol maleate, 12t, 19t
Indirubin, PAH and, 43t
Inflammatory bowel disease, 23t
Inhaled agents, 69t
Inotropes, selection of, 66t
Inspiratory squawks, 26
Inspiratory Velcro crackles, 26, 30, Q30
Insufficient sleep syndrome, 51–52
Intensive Care Delirium Screening Checklist, 60
Intensive care units (ICUs), 58–59, 67–80, Q31, Q71. *See also* Critical care medicine
Interferons, PAH and, 43t
Interstitial lung disease (ILD), 26t, 27, 30–31, Q83
Interstitial pneumonia, 26t
Intraosseous devices, 63–64
Intrauterine infections, 88t
Ipratropium, 12t, 19t
Isopropyl alcohol, 83, 83t

J
Jet lag, 52

L
LABAs (long-acting β_2 agonists), 13, 18, 20, Q13
Lactated Ringer solution, Q35
LAMAs (long-acting muscarinic agents), 18, 18t, 20
Large cell carcinoma, 47, 47f
Leflunomide, 43t
Levalbuterol, 12t, 19t
Light therapy, 52
Light's criteria, 36
Limited cutaneous systemic sclerosis, 43
Lithium toxicity of, 86t
Lorazepam, antidotes for, 85t
Lung biopsies, 27
Lung cancers, 34t, 47–50, Q7, Q51, Q69
Lung sliding sign, 5
Lung transplantation, 21
Lung tumors, 45–47
Lung ultrasonography, 5
Lung volume reduction surgery, Q44
Lung volume reduction therapy, 21
Lymphoma, 39
Lysergic acid diethylamide, 85t

M
Macitentan for PAH, 44t
Macrophages, protease release by, 15
Malignant hyperthermia, 81–82, 81t, Q65
Malignant pleural effusion, 39, Q15, Q91
Malnutrition in critical care patients, Q73
Maxillomandibular advancement, 54
Mediastinal masses, 50–51
Meigs syndrome, 38t
Melatonin, 52
Mepolizumab, 12t, 13
Mesenteric ischemia, 87t
Mesothelioma, 39, 50, Q23, Q81
Metabolic syndrome, 51
Metal-induced lung disease, 34t
Metaproterenol, 19t
Metformin toxicity, 86t
Methamphetamines, 43t, 85t
Methanol, 83, 83t
Methemoglobin, 84
Methicillin-resistant *S. aureus* (MRSA), 24
Methotrexate toxicity, 29t
Methylprednisolone, 12t

Methylxanthines, 20
Mixed connective tissue disease, 28t
Mobilization
    weakness and, 66
Mobilization issues, 60–61, Q1
Modafinil, 52
Mometasone, 12t, 19t
Montelukast, 12t, 15, Q58
Moraxella catarrhalis, 22
Morphine toxicity, 84t
Mounier-Kuhn syndrome, 23t
Mucolytics, 20
Multiple sleep latency tests, 51
Mustard gas, inhaled exposure to, 69t
Myasthenia gravis, 50
Myasthenic crisis, 74
Mycoplasma pneumoniae, 22
Myxedema, 38t

N
Narcolepsy, 51
Nasal cannula, high-flow, 62, Q86
Nasal end-expiratory positive airway pressure device, 54
Nephrotic syndrome, 38t
Neuroleptic malignant syndrome, 81t, 82, Q19
Neuromuscular blockade, prolonged, 67t
Neuromuscular diseases, 56
Neuromuscular weakness, 73–74, 74t, Q95
Neutropenic sepsis, Q18
Neutrophils, protease release by, 15
Nicotine replacement therapy, 17
Nicotine toxicity, 84t
Nintedanib, 30
Nitrites, 84
Nitrofurantoin, toxicity of, 29t
Noninvasive positive pressure ventilation (NPPV), 21, 22, 62–63, 63t
Non-small cell lung cancer (NSCLC), 47, 49
Nonspecific interstitial pneumonia (NSIP), 30–31
Nonspecific pulmonary fibrosis (NSPF), 30–31, 30f
Nontuberculous mycobacteria, 23t
Norepinephrine, 66t, 78
Nutritional support in critical care medicine, Q73, Q92

O
Obesity, 11t, 51
Obesity hypoventilation syndrome (OHS), 55–56, 73, Q49
Obstetric emergencies. *See* Pregnancy
Obstructive lung diseases, 74–75
Obstructive shock, 76t, 77
Obstructive sleep apnea (OSA), 52–54. *See also* Sleep apnea
    asthma and, 11t
    clinical features, 53
    diagnosis of, Q46, Q62
    oral appliances, Q2
    pathophysiology of, 52
    risk factors, 53
    treatment, 53–54
Occupational asthma, 8–9, 34t, Q43
Occupational lung diseases, 33–35
    evaluation of, Q25
    exposure histories, 33–34
    features of, 34t
    management of, 34–35
    screening questionnaire, 33t
    spontaneous pneumothorax and, Q3
    surveillance, 35
Olodaterol, 12t, 19t
Omalizumab, 12t, 13, 14
Omeprazole for GERD, Q81
Opioid-related sleep apnea, Q74
Opioids, 54, 85t
Oral appliances, 54
Organizing pneumonia, 26t, 31
Organophosphates, 69t, 84t
Osborne waves, 82f
Oxidative stress, 15
Oximeters, function of, 3
Oxycodone, 84t, 85t
Oxygen therapy, 20, 22, 62, Q11, Q86
Oxyhemoglobin, 83–84
Oxyhemoglobin desaturations, 52

P
Packed red blood cells (PRBCs), Q53
Pain rehabilitation programs, Q74
Paralytic agents, 70
Paraneoplastic syndromes, 48
Parapneumonic effusions and empyema, 39, Q39
Parenchymal lung disease, 29t, Q20
Parenteral nutrition, 60
PEEP, 69–70
Peptic ulcer perforation, 87t
Peributerol, adverse effects of, 19t
Peripartum cardiomyopathy, 88t
Peripheral venous access, 63
Peritoneal dialysis, 38t
PET/CT, 4t, 5, 46, 49, Q47
Phencyclidine, antidotes for, 85t
Phenylephrine, 66t, 78
Phenylpropanolamine, 43t
Phosgene, inhaled exposure to, 69t
Phosphodiesterase-4 inhibitors, 19t
Phosphodiesterase-5 inhibitors, 44t
Physostigmine toxicity, 84t
Pirfenidone, 30
Placenta previa, 88t
Pleural catheters, Q15
Pleural diseases, 35–41
Pleural effusion, 35–40
    chylorax, 35–40
    evaluation of, 35–36
    exudative, 38t
    in ICU care, Q71
    imaging, 35–36, 36f
    physical examination, 35–36, 35t
    transudates, 38t
    ultrasound, 36f, 37f
Pleural fluid analysis, 36–39, 37t, 38t, Q91
Pleurodesis for pneumothorax, Q4
Pneumococcal polysaccharide vaccine (PPSV23), 20
Pneumoconiosis, 34
Pneumonia
    ARDS and, 71
    bronchiectasis caused by, 23t
    in pregnancy, 88t
    ventilator-associated, 61t
Pneumonia Severity Index, 58
Pneumothorax, 40, 40f, 40t, 41, 58, Q3
Polymyositis, 28t
Polysomnography, 11t, 45, 53–56, Q62
Portopulmonary hypertension, 43
Positive airway pressure therapy, 53–54, 56t, Q38. *See also* Bilevel positive airway pressure (BPAP); Continuous positive airway pressure (CPAP)
Post-intensive care syndrome, 67
Postpyloric feeding, 60
Prednisolone, 12t, 19t, Q64
Prednisone, 12t
Preeclampsia, 88t, Q77
Pregnancy
    asthma in, 15
    critically ill patients, 87, 88
    obstetric critical care emergencies, 88t
    PAH issues in, 43–44
    preeclampsia in, Q77
    pulmonary emboli in, Q27
Primary ciliary dyskinesia, 23t
Prone positioning in ARDS, Q48
Propofol, 59
Prostacyclin analogues, 44t
Prostacyclin receptor agonist, 44t
Pseudomonas aeruginosa, 23, 24
Pulmonary arterial hypertension (PAH), 41–44
    diagnosis, 42f, 43
    drugs and toxins associated with, 43t
    idiopathic, 41f
    management of, 43–44, 44t
    pleural effusions and, 38t
Pulmonary artery catheters, 63
Pulmonary disease, air travel in, 57–58, 57t
Pulmonary edema, 57, 70–71, 88t
Pulmonary embolism (PE), 72
    in pregnancy, Q27
Pulmonary Embolism Severity Index, 58

- Pulmonary fibrosis
    - acute respiratory failure and, 67t
    - asbestos and, 34t
    - DPLD and, 25t, 26t, 71
    - idiopathic, 27, 30–31, 30f, 32f, Q30
- Pulmonary fibrosis and emphysema, combined (CPFE), 31, 32f, Q5
- Pulmonary function testing, 1–3, 1t, 2f
- Pulmonary hypertension (PH), 26, 41–45
    - classification of, 41t
    - diagnosis of, Q78, Q98
    - evaluation of, 42f, 45, Q37
- Pulmonary imaging, 3–5, 4t
- Pulmonary Langerhans cell histiocytosis (PLCH), 27
- Pulmonary nodules, 45–47, 46f, 46t, Q7, Q36, Q47, Q99
- Pulmonary rehabilitation, 20, Q63
- Pulmonary sarcoidosis, Q16
- Pulmonary vascular disease, 41–45
- Pulse oximetry, 3
    - abnormal readings, Q52
    - in airway obstruction, 68
    - in carbon monoxide poisoning, 83–84
    - in ICU, 67
    - overnight, 53
    - oxygen saturation and, 20, 22
    - preflight screening, 58t
    - at rest, 16, 26
- Pure red cell aplasia, 50

Q

- qSOFA scores, 77, 77t
- Q/V mismatch, 72t

R

- Radiation pneumonitis, 28–29, Q70
- Rapeseed oil, 43t
- Rapid response teams, 58
- Reactive always dysfunction syndrome, 9
- Refractory septic shock, Q57
- Residual volume (RV), 3t
- Reslizumab, 12t, 13
- Respiratory bronchiolitis, 26t
- Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), 27
- Respiratory drive, decreased, 73
- Respiratory failure, radiographic findings, 67t
- Restrictive chest wall disease, 74
- Reynolds pentad, Q60
- Rheumatoid arthritis, 23t, 28t
- Riociguat for PAH, 44t, 45
- Risperidone, discontinuation of, Q19
- Roflumilast, 18t, 19t, 20, 22, Q50
- ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*) translocation, 48
- ROX index, 62

S

- Safety Data Sheets, 33t, Q25
- Salicylate toxicity, 86t
- Salmeterol, 12t, 19t
- Sarcoidosis, 26t, 31–33, 32f, 32t, 33t, Q16
- Scopolamine toxicity, 84t
- Sedation
    - in critical care patients, 59–60, 59t, Q31
    - decreased respiratory drive and, 73
- Seizures, obstetric emergencies, 88t
- Selexipag, 44t
- Sepsis, 61t, 75–80
    - adjunctive therapies, 79–80
    - epidemiology of, 78
    - glucose control in, 79–80
    - hour-1 care bundle for, Q68
    - management of, 78–80
    - neutropenic, Q18
    - patient evaluation in, Q55
    - presentation of, 77
    - treatment of, Q35
- Septic shock, 79–80, Q57, Q71
- Sequential Organ Failure Assessment (SOFA), 58, 77, 77t
- Serotonin syndrome, 81t, 82, Q61
- Shift work sleep disorder, 52, Q22
- Shock, 75–77
    - causes of, 76t
    - clinical findings, 75t
    - IV access in, Q59
    - patient evaluation in, Q12
    - transthoracic echocardiography in, Q72
- Short-acting β_2-agonist (SABA), 8, 11, 18
- Sildenafil for PAH, 44t
- Simplified Acute Physiology Score, 58
- Sinus disease, asthma and, 11t
- 6-minute walk test, 2
- Sjögren's syndrome, 23t, 28t
- Sleep apnea, Q62, Q74. *See also* Obstructive sleep apnea (OSA); Central sleep apnea (CSA) syndromes
- Sleep hygiene, 51
- Sleep medicine, 51–56
- Sleep-disordered breathing, 45
- Sleepiness, daytime, 51–52, 51t
- Sleep-related hypoventilation syndromes, 55–56, 55t
- Small cell lung cancer (SCLC), 47, 48f, Q29
- Smoking
    - asthma and, 14, 15
    - cessation of, 17, Q87
    - DPLD and, 27
    - lung cancer and, 48
    - parenchymal lung disease and, Q20
- Smoking-related interstitial fibrosis (SRIF), 27
- Sodium thiosulfate, 84
- Spinal cord injuries, 74
- Spirometry, 1, 7, Q97
- Spontaneous breathing trials, 65t
- Spontaneous pneumothorax, 40, 40t, Q3
- Squamous cell carcinoma, 39, 47, 47f
- St. John's wort, 43t
- Status asthmaticus, 88t
- Steam inhalation, 68
- *Streptococcus anginosus*, 39
- *Streptococcus aureus*, 24, 39
- *Streptococcus pneumoniae*, 22, 39
- *Streptococcus pyogenes*, 39
- Stress ulcer prophylaxis, 59, Q84
- Succinylcholine, Q65
- Sulfonylurea toxicity, 86t
- Surviving Sepsis Campaign, 78–80
- Sympathomimetics, 85t
- Systemic lupus erythematosus (SLE), 28t
- Systemic sclerosis, 28t, 43

T

- Tadalafil for PAH, 44t
- Talc, pleural space obliteration with, 39–40
- Teratomas, 50
- Terbutaline, adverse effects of, 19t
- "Terrible T's," 50
- Theophylline, 12t, 20
- Thermal injuries, 68, Q9
- Thoracentesis, 4t, 5, 35, 36, 39
- Thoracoscopy, 39, 50, Q81
- Thoracostomy, Q4
- Thrombolytic therapy, 72
- Thymomas, 50
- Thyroid tumors, 50
- Tidal volume, decreased, 73–74
- Tiotropium, 12t, 13, 19t, Q8
- Tocolytic therapy, 88t
- Tongue, angioedema of, 80f
- Tonsillectomy, 54
- Total lung capacity (TLC), 1, 3t, 27, 74
- Toxic megacolon, 87t
- Toxicology, 82–86
- Tracheotomy, 54
- Transthoracic echocardiography, 41, 77, Q72
- Treprostinil for PAH, 44t
- Tricyclic antidepressants, toxicity of, 84t, 86t
- Triglycerides, pleural effusions and, 39
- L-tryptophan, 43t
- Tuberculosis, 23t, 39

U

- Ultrasonography
    - lung, 5
    - point-of-care, Q28
    - point-of-care in shock, 75, 77, Q12
    - pulmonary imaging, 4t
    - thoracic, 35–36
- Umeclidinium, 12t, 13, 19t

Unexpandable lung, 38t
Upper airway patency, 52, 56t
Urinothorax, 38t
Uterine atony, 88t
Uterine rupture, 88t
Uvulopalatopharyngoplasty, 54

V
Vaccinations, 20
Vaping, 68–69
Vasopressin, 66t, 78
Vasopressors, 66t, 78, 79
Venous access in shock, 63–64, 65t, Q59
Venous thromboemboli, 88t
Ventilation, mechanical, 62–63. *See also* Noninvasive positive pressure ventilation (NPPV)
  extubation, 62–63, 64t, 65t
  general principles, 62–63
  modes, 64t
  sedation and, 59–60, 59t
  weaning from, 61, 63, 65t
Ventilator-associated pneumonia, 61t
Ventilatory failure, 61. *See also* Hypercapnic respiratory failure
Ventilatory overshoot, 54, 57
Vilanterol, 12t, 19t
Vitamin E acetate, 68
Vocal cord dysfunction (VCD), 8, 9, 11t
Volume overload, 70
Volutrauma, 63, 69
V/Q mismatch, 68, 70, 72–74, Q10

W
Workers' compensation, 34–35
Wrist actigraph, 51

Y
Young syndrome, 23t

Z
Zafirlukast, 12t, 15
Zileuton, 12t